Impact of pulmonary rehabilitation on patients with interstitial lung diseases: an Egyptian experience

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Background Dyspnea, cough, fatigue, functional limitation, and low quality of life (QOL) are manifestations of almost all interstitial lung diseases (ILDs), with little effective and may be well-tolerated pharmacotherapy in most of its subtypes. The application of pulmonary rehabilitation (PR) may have some benefits in patients with ILDs.

Aim The aim of this study was to evaluate the effect of PR program on ILD patients' QOL, exercise capacity, dyspnea, and spirometry.
Settings and design This was a single-center experimental randomized controlled study.

Patients and material This study initially enrolled 62 patients previously diagnosed as having ILD at the Chest Department according to American Thoracic Society (ATS)/ European Respiratory Society (ERS) diagnostic criteria; however, 12 patients were excluded, and only 50 patients were included and completed the study, and they were classified randomly into the control group (*n*=25, received conventional treatment only) and the PR group (*n*=25, received conventional treatment and PR). Pre-PR and post-PR program assessment of QOL by the 36-item short-form health survey (SF36) questionnaire, exercise capacity by the 6-min walk test, dyspnea by the modified Medical Research Council and spirometry were carried out.

Statistical analysis used All data were collected, tabulated and statistically analyzed using SPSS 16.0 for Windows.

Results This study showed a statistically significant difference for the PR group over the control group at the end of the PR program, wherein all components of the SF36Q score had a *P* value less than 0.05, dyspnea score by modified Medical Research Council (*P*=0.02) and exercise tolerance by 6 min walking distance test (*P*=0.005). Moreover, the maximum voluntary ventilation (MVV%) showed a statistically significant improvement (*P*=0.003) in contrast to the other measured spirometric parameters measured in this study (forced vital capacity, forced expiratory volume in 1 s, forced expiratory volume in 1 s/forced vital capacity %, forced expiratory flow$_{25–75}$) wherein *P* value was more than 0.05. A negative correlation was found between the baseline physical functioning item of SF36Q and the change (Δ) in 6 min walk distance test.

Conclusion PR could be considered as an adjuvant method in the treatment of patients with stable ILDs and could provide improvement in their dyspnea perception, exercise tolerance, and health-related QOL.

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Introduction

Dyspnea, cough, fatigue, functional limitation, and low quality of life (QOL) are manifestations of almost all interstitial lung diseases (ILDs) with little effective and may be well-tolerated pharmacotherapy for most of its subtypes [1]. Moreover, skeletal muscle dysfunction, weakness, and atrophy lead to worsening of exercise capacity and increasing symptoms [2,3]. The application of pulmonary rehabilitation (PR), which is best described in COPD patients, can be also of some benefit in patients with ILDs [4], and this was recommended by some recent clinical studies for its management; however, the number of studies supporting its value was low with unclear long-term benefits [5]. The impact of the disease on physical, psychological, and social functioning is related to the term health status, whereas evaluation or perception of their function is the QOL, which is totally a subjective matter [6–8]. Despite the promising benefits of PR for ILD patients, it is underused to help those poor patients combat the disabling effects of such a disease by improving skeletal muscle power, exercise tolerance, and psychosocial state [9].

Aim

To evaluate the effect of PR program on ILD patients' QOL, exercise capacity, dyspnea, and spirometry.

Study design

A single-center experimental randomized controlled study.

Patients and methods

This study was carried out at Pulmonary Rehabilitation Unit of Chest Department, Zagazig University hospitals, after obtaining the approval of the Institutional Review Board, Zagazig University.

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Patients

This study initially enrolled 62 patients previously diagnosed as having ILD at the Chest Department according to American Thoracic Society (ATS)/ European Respiratory Society (ERS) diagnostic criteria [10]; however, 12 patients were excluded from the study (10 patients refused to continue the program due to difficulty of transportation and regular attendance during the period of the program, and two patients died). Only 50 patients were included and completed the study. The patients were classified randomly and equally into two groups:

(1) PR group (n=25) who received the conventional pharmacological therapy for ILDs (oral steroids, e.g. prednisolone, acetyl-cysteine, and/or immunosuppressive drugs, e.g. azathioprine) in addition to PR.
(2) Control group (n=25) who received only the conventional pharmacological therapy for ILD.

Inclusion criteria

All patients having stable ILD (no exacerbations 4 weeks before starting PR program and under regular conventional therapy) were included[11]. Acute exacerbation of ILD was defined as a rapid worsening of respiratory symptoms with increased dyspnea within less than 1 month [12].

Exclusion criteria

History of syncope on exertion or any comorbidities that counteract PR, for example, severe orthopedic or neurological deficits or unstable cardiac disease or severe pulmonary hypertension (mean pulmonary artery pressure (mPAP) ≥55 mmHg]. Patients were also excluded if they had participated in a PR program in the past 12 months [1,13,14].

Methods

Baseline arterial blood gases (ABGs) (RapidlabTM 348; Bayer Health Care; RAPIDLab® 348EX Blood Gas System, Siemens Healthineers Global), spirometry (winspiropro 5), modified Medical Research Council (mMRC), 6 min walk distance test (6MWDT) and QOL by the 36-item short-form health survey (SF36) questionnaire were assessed for all pparticipants on the first day (before the randomization of the studied patients) and last scheduled day of the PR program at the PR unit [15].

The PR group was subjected to the PR program for 8 weeks wherein they attended the PR unit twice weekly (supervised PR sessions) and an unsupervised home exercise program for a further 3 days with a total five exercise sessions per week [1,14]. The PR program was performed according to standard ATS/ERS recommendations [1,16], which included the following aspects:

(1) Patient health education.
(2) Physical exercise including what follows:
    (a) Upper and lower limb exercise training:
        (i) Interval endurance exercise training by cycle ergometer (LonGstylE) and arm wheel: (a) the exercise intensity targets were 80–100% of maximum heart rate in the first three to four sessions, and then it was increased gradually by 5–10% to reach 150% according to patients' ability to tolerate exercise. (b) Type of exercise was interrupted with equal periods of rest and periods of exercise. (c) Time of exercise was 30–180 s with equal periods of rest. (d) Duration of exercise was 15–20 min in the first three to four sessions, then it was increased progressively to 45–60 min (including resting time).
        (ii) Resistance/strength training:
        This included the use of free weights, Thera-Band, and ball exercise for the upper limb according to American College of Sports Medicine guideline.
        The exercise intensity targets were 50–85% of one repetition maximum load, one that evokes fatigue after 8–12 repetitions are appropriate then load was increased, if patient can do current workload for one to two sessions by increase resistance or weight increase repetitions/set, increase number of set/ exercise or decrease rest period between sets of exercise. The duration of exercise was two to four sets of 6–12 repetitions. During both endurance and resistance/ strength training, monitoring of oxygen saturation with supplemental oxygen was provided during training if necessary to achieve oxygen saturation more than or equal to 85%, heart rate, mMRC grading, and limb fatigue during every exercise training session.
        End of exercise: mMRC grading more than or equal to 3 or muscle fatigue.
    (b) Respiratory muscles' exercise: (a) pursed-lip breathing in which the patient inhales through the nose with mouth closed, exhales

through mouth lips pursed tightly. (b) Diaphragmatic breathing in which patient inhales slowly through nose with the abdomen expanding outwards and exhales slowly through pursed lip while drawing abdomen inward. (c) Incentive spirometry: this was carried out by using three-ball, flow-measuring device Plasti-med Three ball.

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS, 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as the mean±SD and median (range), and qualitative data were expressed as absolute frequencies (number) and relative frequencies (percentage). Continuous data were checked for normality by using Shapiro–Wilk test. Independent Student's *t* test was used to compare two groups of normally distributed data, whereas the Mann–Whitney *U* was used for non-normally distributed data. Percent of categorical variables were compared using χ^2 test or Fisher's exact test when appropriate. All tests were two sided; *P* value less than 0.05 was considered statistically significant; *P* value less than 0.001 was considered highly statistically significant, and *P* value more than or equal to 0.05 was considered nonstatistically significant.

Results

Fifty patients from the initially chosen 62 ILD patients were enrolled in the study and randomly divided into two groups, the PR group which included 25 patients and the control group which included the other 25 patients. The baseline data of the studied population, which is shown in Table 1, showed that there was no statistically significant difference between cases of the PR group and their controls with regard to sociodemographic characters, pre-PR health-related QOL questionnaire (the 36-item SF36), pre-PR 6-min walk test, and dyspnea score by mMRC dyspnea score, wherein the range of pretreatment dyspnea score by mMRC was the same (1–3) in both groups and the range of pre-PR 6MWDT was 300–510 versus 300–520 m in the PR group and the control group, respectively, with no statistically significant difference. ILD patients included 12 idiopathic pulmonary fibrosis, seven (28%) patients in the PR group and five (20%) patients in the control group; 18 connective tissue diseases, eight (32%) in the PR group, 10 (40%) in the control group; 20 hypersensitivity pneumonitis, 10 (40%) in the PR group and 10 (40%) in the control group. There was no statistically significant difference in pre-PR spirometry parameters for both groups, wherein the pre-PR forced vital capacity (FVC) range was 54–60% of predicted versus 55–58% of predicted in both the PR group and control group, respectively, and the range of forced expiratory volume in 1 s (FEV_1)/FVC% was 105–112% of predicted versus 106–115% of predicted. Moreover, FEV_1 range was 70–78% of predicted versus 72–80% of predicted in both the PR group and the control group, respectively; forced expiratory flow ($FEF_{25–75}$) range was 41–87% of predicted versus 45–86% of predicted in both the PR group and the control group, respectively. Maximum voluntary ventilation (MVV) range was 81–92% of predicted versus 52–92% of predicted in both the PR group and the control group, respectively (Table 2). A statistically significant difference was present between both patients' groups with regard to the post-PR program and improvement in all components of SF36Q score ($P<0.05$) (Table 3). This study revealed a statistically significant improvement in dyspnea score by mMRC ($P=0.02$) and exercise tolerance by 6MWDT ($P=0.005$) in the PR group compared with the control group. Moreover, the MVV% showed a statistically significant improvement ($P=0.003$) compared with the other measured spirometric parameters measured in this study (FVC, FEV_1, FEV_1/FVC%, $FEF_{25–75}$) wherein *P* value was more than 0.05 (Table 4). A negative correlation was found between the baseline physical functioning item of SF36Q and change (Δ) in 6MWDT, which was illustrated in Fig. 1.

Discussion

Skeletal muscle dysfunction and atrophy in ILDs have many factors like chronic hypoxemia, inflammatory and oxidative stress, physical rest, malnutrition, and physical inactivity in addition to the use of corticosteroids [17]. The current study aimed to evaluate the effect of PR on ILDs' patients with different aetiologies in Zagazig City of Egypt to add evidence to other previous worldwide studies to provide a solid evidence-based application of PR program for those patients. Despite the diversity of ILD etiology, the proposed benefits of PR were evaluated in a trial to help those patients to improve their QOL and relieve symptoms by the addition of muscle training as a line of treatment that was evaluated [1,11,15]. Upper and lower limb muscles' training was the main target in many studies, even the recent one by Dowman *et al.* [1] and the old one, which was carried out by Holland *et al.* [14], but they neglect the vital role of respiratory muscles' exercise, especially the diaphragmatic training,

Table 1 Baseline data of the studied population and prepulmonary rehabilitation health status evaluation by short-form health survey questionnaire, exercise by 6 min walk distance and dyspnea by modified Medical Research Council

Variables	Groups [*n* (%)]		χ^2	*P* value
	PR group (*N*=25)	Controls (*N*=25)		
Male	8 (32)	10 (40)	0.347	0.769 NS
Female	17 (68)	15 (60)		
Age (mean±SD)	47.3±12.7	48.8±10.14	0.468[t]	0.642 NS
Types of ILD				
IPF	7 (28)	5 (20)	0.483	0.749 NS
CTDs	8 (32)	10 (40)		
HSP	10 (40)	10 (40)		
6MWDT				
Mean±SD	422.1±56.7	424±56.9	0.00[t]	1.0 NS
Range	300–510	310–520		
mMRC				
Mean±SD	2.23±0.78	2.12±0.78	0.544[#]	0.595 NS
Range	1–3	1–3		
Physical functioning				
Mean±SD	51±16.4	48.5±14.4	0.536[#]	0.681 NS
Range	25–75	25–75		
Limitation due to physical health				
Mean±SD	38±39.5	39±39.6	0.09[#]	0.928 NS
Range	0–100	0–100		
Limitation due to emotional problems				
Mean±SD	41.9±31.6	42.3±33.4	0.05[#]	0.959 NS
Range	0–100	0–100		
Energy/fatigue				
Mean±SD	53.7±19.01	54±17.4	0.07[#]	0.946 NS
Range	10–80	10–80		
Emotional well being				
Mean±SD	46.6±19.5	46.7±19.6	0.03[#]	0.977 NS
Range	17.5–34	17.6–34		
Social functioning				
Mean±SD	57.1±22.1	53.6±22.8	0.555[#]	0.823 NS
Range	25–87.5	25–87.5		
Pain				
Mean±SD	53.4±19.3	48.7±21.8	0.807[#]	0.424 NS
Range	22.5–77.5	22–77.5		
General health				
Mean±SD	45.96±15.9	43.1±14.4	0.662[#]	0.511 NS
Range	20–80	20–8		

[x,] χ^2 test. [t,] *t* test (comparing mean values of both groups). #Mann–Whitney test for nonparametric data. [6] MWDT, 6 min walk distance test; CTDs, connective tissue diseases; HSP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; mMRC, modified medical research council; PR, pulmonary rehabilitation.

which was included in the PR program of this study according to standard ATS/ERS recommendations [16]. This was in agreement with the recent study of Tonelli *et al.* [18] who included breathing training in their study. This study had chosen an 8-week duration of PR program with a twice weekly attendance at the PR unit in accordance with many studies [14,19,20] and nearly in accordance with Dowman *et al.* [1] who chose a 9-week program. Some other studies selected a shorter or longer program duration like that of Holland *et al.* [20] wherein the range was 5–12 weeks with a median of 10 weeks. The 6MWD, mMRC, and SF36Q for QOL were chosen to evaluate the expected benefits of the PR program for ILDs' patients. The demographic and baseline data showed a nonsignificant difference, confirming the matching between the two groups, and was in accordance with many studies like that of Tonelli *et al.* [18]. Despite the small sample size in this study (50), which was also present in previous studies, for example, 57 [14], 44 [21], and 18 [19], there was a statistically significant improvement in 6MWD, mMRC, and SF36Q for QOL, which strengthens the rationale for PR to be recommended as a standard, available, cheap, and safe treatment in ILD patients, regardless the etiology. The improvement in exercise

Table 2 Comparison between both groups as regards prepulmonary rehabilitation spirometric parameters

Variables	Groups		*t* test	*P* value
	PR (*N*=25)	Control (*N*=25)		
FEV_1% of predicted				
Mean±SD	75.1±3.23	76.1±3.03	1.31	0.07 NS
Range	70–78	72–80		
FVC % of predicted				
Mean±SD	56.8±1.93	57.1±1.99	0.432	0.668 NS
Range	54–60	55–58		
FEV_1/FVC %				
Mean±SD	108.3±3.23	109.4±3.03	1.34	0.07 NS
Range	105–112	106–115		
$FEF_{25–75\%}$ of predicted				
Mean±SD	61.5±14.5	61.8±14.6	0.09	0.958 NS
Range	41–87	45–86		
MVV % of predicted				
Mean±SD	86.2±4.45	84.6±8.04	0.892	0.373 NS
Range	81–92	52–92		

t test, comparing mean values of both groups. FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PR, pulmonary rehabilitation.

Table 3 Statistical comparison between postpulmonary rehabilitation parameters in both studied groups as regards the change in health status evaluation by short-form health survey questionnaire

Variables	Groups		*t* test MW#	*P* value
	PR (*N*=25)	Control (*N*=25)		
Physical functioning				
Mean±SD	57.2±16.8	46.6±12.3	3.96	0.04*
Range	30–82	25–70		
Limitation due to physical health				
Mean±SD	43.3±39.8	36.8±37.6	4.39#	0.02*
Range	3–107	0–100		
Limitation due to emotional problems				
Mean±SD	48.1±33.8	40.3±30.4	4.64#	0.01*
Range	5–106	0–100		
Energy/fatigue				
Mean±SD	66.8±19.3	54±17.4	2.47	0.02*
Range	22–94	10–80		
Emotional well being				
Mean±SD	59.9±29.7	45.9±20.2	2.23#	0.04*
Range	24–95.5	17.6–34		
Social functioning				
Mean±SD	10.8±1.28	4.6±1.23	6.96	0.004*
Range	9–12	2–6		
Pain				
Mean±SD	60.7±19.9	48.7±21.8	2.04#	0.04*
Range	27.5–86.5	22–77.5		
General health				
Mean±SD	50.1±16.01	38.5±12.1	3.78	0.04*
Range	23–84	20–80		

t test, comparing mean values of both groups. #Mann–Whitney *U* test for nonparametric data. PR, pulmonary rehabilitation. **P* value less than 0.05 is significant (S).

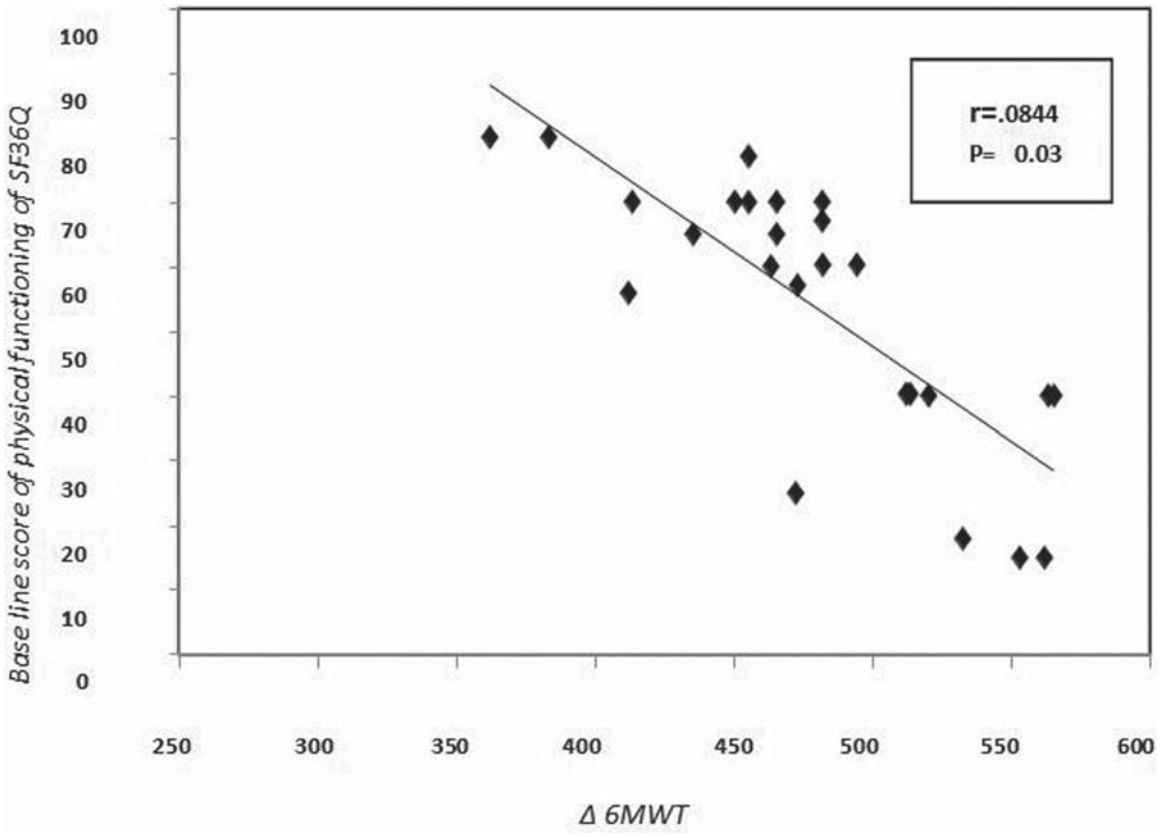
capacity evidenced by 6MWD in the current study was in accordance with many previous studies like that of Nishiyama *et al*. [22], Perez *et al*. [23], and Vainshelboim *et al*. [24]. Moreover, Collard *et al*. [25] found that the improvement in 6MWD in the PR group was comparable to the improvement by usage of sildenafil in idiopathic pulmonary fibrosis patients. On the contrary, Holland *et al*. [14] reached a smaller degree of improvement, which was statistically nonsignificant. The improvement in dyspnea in this study by mMRC evaluation was matched with Tonelli *et al*. [18], Baradzina *et al*.

Table 4 Comparison between both studied groups as regards postpulmonary rehabilitation change in dyspnea score by modified Medical Research Council, 6 min walk distance test, and change in spirometric parameters

Variables	Groups		t- test	*P* value
	PR (*N*=25)	Control (*N*=25)		
Post ttt in 6MWDT (mean±SD)	478.5±54.1	433.04±56.1	2.92	0.005*
Post ttt mMRC (mean±SD)	1.72±0.84	2.28±0.79	2.42#	0.02*
Post ttt. FEV_1% L (mean±SD)	76.5±0.87	76.7±0.85	0.981	0.329
Post ttt FVC% L (Mean±SD)	58.3±1.7	56.88±1.51	1.37	0.234
Post ttt FEF_{25-75}% L (mean±SD)	62.6±14.25	61.4±14.19	0.276	0.768
Post ttt. FEV_1/FVC % (mean±SD)	115.8±7.9	113.9±6.34	1.04	0.234
Post ttt MVV% (l/min) (mean±SD)	90.7±6.63	84.2±8.2	3.11	0.003*

#Mann–Whitney test for nonparametric data. 6MWDT, 6 min walk distance test; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council; PR, pulmonary rehabilitation; ttt, treatment. **P* value less than 0.05 is significant.

Figure 1



Scattered plot with regression line shows negative correlation between baseline physical functioning item of SF36Q and Δ6MWDT. 6MWDT, 6 min walk distance test; SF36Q, short-form health survey questionnaire.

[26], Vainshelboim *et al.* [24], and Dowman *et al.* [11] who demonstrated a decline in mMRC score with statistically significant difference –after the PR program. The current study investigated the possible effect of PR on some spirometric parameters, for example, FVC% predicted, wherein there was no statistically significant difference between the PR group and the control group, which was in accordance with Nishiyama *et al.* [22]. On the contrary, Huppmann *et al.* [27] found that there was a marginal improvement in FVC%. This study investigated the FEV_1% of predicted, FEV_1/FVC%, FEF_{25-75}%, and MVV% of predicted (which is a good parameter for global respiratory muscles' function). All of them showed nonsignificant statistical difference, except for MVV %, which was improved in the PR group, which may reflect the global improvement of respiratory muscles that had occurred in the PR group. These data, combined with previous studies [15], give a solid evidence-based recommendation for the pulmonologist to send their patients with ILD early, regardless the etiology, for PR programs to improve QOL, dyspnea, exercise capacity, and MVV.

Conclusion

PR could be considered as an adjuvant method in the treatment of patients with stable ILDs and could provide improvement in their dyspnea perception, exercise tolerance, and health-related QOL.

Limitations of the study

The limitations of this study were the obstacles and difficulties of transportation of the patients to attend the PR program (10 patients); hence, home-based PR programs may be more helpful and more beneficial by usage of recent video telecommunication (telerehabilitation) to supervise and guide the exercises.

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Nil.

Conflicts of interest

There are no conflcits of interest.

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