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The Role of Pulmonary Rehabilitation in Patients with Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is known as one of the most severe lung conditions and the worst form of interstitial lung disease (ILD). There is a continuing concern about clinical research to identify new therapies that influence the quality of life in patients diagnosed with this chronic progressive pulmonary disease, with an average survival of 3–5 years. Although in recent years great progress has been made to slow down the functional decline of the disease with new antifibrotic therapies, it has failed to alter the prognosis and survival of IPF patients. Clinical trials and recent ATS/ERS guidelines have brought at least moderate and low levels of evidence for increased effort tolerance, decreased symptoms, and improved quality of life following participation in lung rehabilitation programs for ILD patients and in particular those with IPF. Pulmonary rehabilitation has been shown to be a standard of care for COPD patients, but their personalized application to patients with IPF has had positive short-term results, becoming a safe alternative to non-pharmacological treatment. The chapter includes the general objectives of rehabilitation programs, their type and structure, ways of complex assessment of patients before and after a training exercise, types of exercises, and short- and long-term results.

Keywords: idiopathic pulmonary fibrosis (IPF), pulmonary rehabilitation program (PRP), physical activity, exercise training, quality of life

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic disease that affects exclusively the lung, with an unknown etiology and a fast-progressive irreversible evolution, therefore disabling the adult. For most of the patients, the average survival is approximately 3–5 years from diagnosis [1, 2]. With an unpredictable but progressive evolution (slower, stable, or accelerated decline from patient to patient), the disease is characterized by a chronic presence of symptoms, specifically the exertional dyspnea, low tolerance to effort, and the deterioration of the quality of life [1–4]. The diagnosis of the disease is often delayed and not reported until advanced stages [5]. A hope to halt the progression of the disease occurred with the demonstration of the reduction in the functional decline of the new pharmacological agents, pirfenidone and nintedanib, without claiming to cure the disease [1–5]. IPF remains a life-threatening illness in which the patient is fighting for survival as long

as possible, striving to cope with the symptoms and the noticeable fatigue. Given that this is a fatal disease, some of the needs identified in patients with IPF and their families are easy access to information and IPF specialists, the existence of more treatment methods, emotional support, and access to end-of-life care [3].

The indication of pulmonary rehabilitation (PR) for patients with IPF came from the positive results stemming from the exercise training program (ETP) in COPD. Thus, numerous clinical studies performed on patients with IPF proved that their health and wellness could be improved, at least for short periods, through ETP which are personalized and supervised by specialists [2].

Pulmonary rehabilitation program (PRP) is an evidence-based recommendation for the non-pharmacological treatment of patients with chronic pulmonary diseases, especially for COPD, but also for interstitial lung diseases [1, 4]. PRP must be included in the integrative treatment of IPF, taking into consideration the severity of the disease, high mortality during exacerbations, a modest response to new drugs, and accelerated deterioration of lung function.

2. The indication of pulmonary rehabilitation starting from pathophysiology in IPF

The usual interstitial pneumonia (UIP) pattern (fibrosis with collagen and matrix deposition, the presence of fibroblastic foci and alveolar collapse, pulmonary heterogeneous architectural distortion and honeycombing presence) determines the main pathophysiological changes in IPF: loss of lung volume, decreased lung compliance, abnormal pulmonary gas exchange with oxygen diffusion limitation, low mixed venous oxygen content, circulatory impairments, and alveolar ventilation/perfusion ($V'A/Q'$) mismatching [6, 7].

Pulmonary function tests reveal restrictive pulmonary dysfunction, indirect signs of increased elastic recoil, and decrease in diffusion capacity for carbon monoxide (DLCO). Pulse oximetry and arterial blood gases reveal hypoxemia initially only during exercise and, in advanced cases, as well during resting [2, 7]. Patients with IPF have reduced maximal or peak oxygen uptake ($V'O_{2peak}$), peak work rate, and submaximal exercise endurance [7].

The progressive installation of morphophysiopathological changes is reflected in the clinical symptoms of patients. The exertional dyspnea is the first and most important symptom of IPF patients. The more advanced the disease, the more severe the dyspnea is. The patients tend to be less physically active and more depressed [8]. The level of dyspnea is strongly correlated with the exercise capacity, the quality of life, and mortality [1, 8, 9]. Other associated symptoms are fatigue, dry cough, chest discomfort, and leg pain. These symptoms are mild or inconsistent at the beginning of the disease, but they get worse over time and lead to an impairment of daily activities [10]. Symptomology and physical inactivity are directly related to depression, quality of life (QoL), and increased mortality [10, 11].

Consequently, the most important mechanisms that limit effort capacity and change the IPF patient's lifestyle, into a sedentary one, are inefficient breathing mechanics, abnormal pulmonary gas exchange, circulatory impairment, and exercise-induced hypoxemia [1, 7, 12, 13]. In time, progressive exercise-induced hypoxemia leads to respiratory and skeletal muscle dysfunction [1, 7]. Non-pharmacological interventions must take into account these mechanisms and create programs that seek to influence the patients' outcomes positively. PR is a safe and effective non-pharmacological treatment [14].

The official ERS/ARS statement define pulmonary rehabilitation as "Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient

assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors” [11].

PR decreases dyspnea, improves exercise capacity, and helps to cope with functional activities of daily life in IPF patients, even though the significance of these benefits is smaller and lasts for less time than in other chronic lung disease like COPD [15–20].

3. General objectives of pulmonary rehabilitation in IPF

- Decreasing symptoms, especially dyspnea
- Increasing effort capacity
- Enhancing the quality of life, health, and wellness
- Improving muscle strength and endurance
- Maintaining joint mobility
- Increasing tolerance to physical activity with the improved cardiometabolic and respiratory profile
- Improving well-being and cognitive functions
- Decreasing depression and anxiety
- Offer social and psychological support with the possibility of occupational and group therapy
- Promoting pro-healthy behaviors, with decreasing effort deconditioning
- Self-management of the disease [20–22]

The adaptation of pulmonary rehabilitation programs for IPF started from those applied to patients with COPD. It is advised to take into account the pathophysiology mechanisms particular to IPF and the clinical particularities of these patients. Patients have a respiratory pattern of frequent, superficial, and rapid breaths that worsen during exercise [7, 17, 18]. The frequent association of pulmonary hypertension (PH) aggravates the symptoms [1, 4]. An explanation for the positive results of PRP could be that repetitive ventilator stimulus during physical training sessions increases chest expansion and secondary pleural elasticity and pulmonary compliance while also improving V'A/Q' mismatch, increasing V'O_{2peak} [13, 23]. Also, deep breathing exercises with stretching and the training of respiratory muscles, including the diaphragm, can help to reduce dyspnea [20, 23, 24].

4. Assessment of IPF patients before and after PRP

Before entering into a PRP, patients with IPF need to be assessed by the multidisciplinary team regarding clinical and functional status, imaging, effort tolerance,

quality of life, physical activities of daily living (PADL), the presence of comorbidities, needs, and expectations from the pharmacological treatment. The evaluation of comorbidities such as coronary arterial disease, systemic and pulmonary hypertension, right and left ventricle dysfunction, and arrhythmias during exercise is critical. The additional impairment of the cardiovascular system decreases the effort capacity and worsens dyspnea and prognosis of patients [1, 2, 25]. This complex assessment also has the role in determining the type, intensity, and results of the PRP.

4.1 Symptoms assessment

Dyspnea is the most significant and disabling symptom for IPF patients. It can be objectively identified before, in the end, and at any time within PRP and can modulate the intensity of exercise. In studies targeting PR in IPF, dyspnea is quantified using one of the following scales:

4.1.1 Modified Medical Research Council (MMRC)

The *Modified Medical Research Council (MMRC)* scale is a well-known tool which assesses the dyspnea based on 5 degrees that are reported by the patient depending on his physical activity tolerance. It seems that dyspnea severity correlates with lung function parameters and Saint George Respiratory Questionnaire (SGRQ). The patient identifies the number that best matches his/her shortness of breath [26–28]. The standardized mean difference (SMD) for change in dyspnea in favor of exercise training (ET) is considered to be -0.66 (95% CI= -1.05 - 0.28) [15]. MMRC dyspnea scales reflect the severity of the limitation of daily activity, pulmonary function, and quality of life and correlate with mortality. It can replace, where it is not possible to assess, the peripheral muscle strength, functional exercise capacity, and ADL performance [29].

4.1.2 University of California, San Diego Shortness of Breath Questionnaire (UCSD SOB)

The *University of California, San Diego Shortness of Breath Questionnaire (UCSD SOB)* uses a 24 questions questionnaire about the level of dyspnea during daily activities [30]. Five points represent a significant mean difference [31]. Dyspnea measured by UCSD SOB showed the strongest correlations with 6MWD [32].

4.1.3 Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI)

The *Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI)* assesses on a 5-degree scale (from 0 to 4), the daily dyspnea level in response to three categories of questions on functional impairment, the magnitude of task, and the magnitude of effort [26, 33, 34]. TDI records the changes from the initial value, the total score varying between -9 (worsening) and $+9$ (improvement). The significant minimal difference between TDI is 1 point [33, 34].

4.1.4 Modified Borg Scale (MBS)

The *Modified Borg Scale (MBS)* has 10 points (from 0 to 10), where participants choose descriptive terms that best suit their current state (0 = no dyspnea, 5 = moderate dyspnea, 10 = very severe dyspnea). It is used before and after performing a submaximal effort test such as 6MWT. The standardized significant mean difference (SMD) for change is 1 point [31]. During exercise training sessions in the PRP, the Borg scale is used as an essential tool to recommend workload [35].

It was shown that there are correlations between clinical dyspnea rating and exercise capacity, exercised gas exchange and exercise capacity, and SGRQ in patients with IPF [26, 29, 36].

4.2 Pulmonary function tests

Pulmonary function tests, including forced vital capacity (FVC), total lung capacity (TLC), maximal voluntary ventilation (FEV1 x 35), and diffusion capacity for carbon monoxide (DLCO), are important for stratifying the severity of the patient's condition, but generally, PRP does not significantly influence the results of these tests [20]. The severity of dysfunction may guide the type and intensity of physical exercise and may be a warning about the risk of adverse effects (severe hypoxemia, hypotension, arrhythmias, etc.)

4.3 Standardized effort tests

Standardized effort tests are important for choosing the intensity of training programs.

4.3.1 The 6-minute walking test (6MWT)

The 6-minute walking test (6MWT) is a simple and safe tool used for IPF patients, where the subject moves in his rhythm [37]. It is performed according to ATS guidelines in a 30-m corridor [38]. 20–30 min of rest is recommended before and after the 6MWD test. The blood pressure, heart rate, respiratory frequency, oxygen saturation (SpO₂), the severity of dyspnea, and fatigue are assessed by the modified Borg scale [38, 39]. SpO₂ is recorded in the sitting position. It is recommended that the 6MWD test be performed with a SpO₂ Holter, to record the length of the desaturation and the lowest value of oxygen [40]. It is always necessary to take into consideration the contraindications of walking tests and also the indications of interruption of the test. An important cessation criterion is a desaturation below 85% or tachycardia [80% of the theoretical maximum heart rate ($220 - \text{age}$)], a situation easily met in IPF patients [1, 41]. The distance covered by the patient in 6 minutes is compared with the predicted value estimated by the formulas (women: $493 + (2.2 \times \text{height (cm)}) - (0.93 \times G \text{ (kg)}) - 5.3 \times \text{age (years)}$ and for the male $+ 17 \text{ m}$). The lower limit of normal 6MWD is the theoretical distance minus 100 m [42–44]. The 6-minute walk test distance (6MWD) does not correlate with sex, age, body mass index, and other medical comorbidities, but it is an independent predictor of survival rate, better than FVC and DLCO [37]. The 12-minute walk test is less used for IPF patients because it requires greater effort.

The minimal clinical important significant difference (MCID) for 6MWD varies with the author, but a change of approximately 30 m is considered to be significant in IPF patients [32, 41, 44, 45].

4.3.2 Cardiopulmonary exercise tests

Cardiopulmonary exercise tests, when available, provide details on the mechanisms of effort intolerance. Measures of the anaerobic threshold, peak oxygen consumption ($\dot{V}O_{2\text{peak}}$), and peak work rate (WR) are essential for determining the intensity of PRP and for assessing the benefits in dynamics. The SpO₂, blood pressure, and 12-lead electrocardiogram are also recorded during these tests [46]. Cardiopulmonary stress tests are the gold standard for assessing the effort intolerance due to either lung, cardiac, or musculoskeletal pathologies. It is performed with a cycle ergometer

or treadmill, but there is also a portable metabolic device. Cycle ergometry is the preferred method of being safer, with few movement artifacts, allowing a constant increase in workload, and is slightly influenced by weight [46–48]. Treadmill testing involves a kind of effort more common to patient's daily activities (walking and running) and can train more muscle mass. Therefore, the $\dot{V}O_{2\text{peak}}$ is 5–10% higher than in cyclo-ergometry. Effort tests have a role in selecting patients for PRP and establishing rehabilitation design protocols, as well as evaluating outcomes [48].

In patients with advanced IPF, it is not always possible to perform cyclo-ergometry. Volitional fatigue or increased oxygen desaturation ($\text{SpO}_2 < 80\%$) is quickly reached, and dizziness or mental confusion may also occur within 10–12 min of effort [48]. The incremental exercise testing shows decreased aerobic capacity ($\dot{V}O_{2\text{peak}} \sim 62\%$ from predicted) and reduced maximal achievable workload in ILD. Other changes in IPF patients such as inefficient ventilation, desaturation, gas exchange abnormalities, circulator, and skeletal muscle dysfunction are reported [2]. These changes provoke a downward spiral of hypoxia, limited exercise capacity, deconditioning, shallow breathing pattern, and pulmonary hypertension [48].

4.4 Doppler-echocardiographic assessment

Doppler-echocardiographic assessment of pulmonary artery systolic pressure should be assessed because a significant percentage of the IPF patients develop PH from early stages of the disease [10, 49]. It represents an important prognostic parameter [10, 49]. It usually replaces right heart catheterization, echocardiography being a noninvasive and widely available tool for screening PH. A substantial desaturation during exercise or a disproportionate exercise limitation related to the degree of lung restriction will increase the suspicion of PH [7, 10].

4.5 Chest high-resolution computed tomography (HRCT) and lung ultrasound

HRCT is the essential method to diagnose IPF. If the HRCT shows a pattern of usual interstitial pneumonia (UIP), this being the most characteristic to IPF, then its presence avoids invasive procedure such as lung biopsy. In the last few years, radiation-free techniques, such as the lung ultrasound, appear to be very sensitive in detecting fibrotic change or monitoring disease progression [50]. Imaging on HRCT is important and significant before a PRP, but its rehabilitation benefits are not assessed according to the initial findings.

4.6 Physical activity of daily living (PADL)

Physical activity of daily living (PADL) has a major impact on the quality of life and well-being of IPF patients and needs to be evaluated. PADL refers to volunteer movements that the patient performs at home, during professional or recreational activities that are energy-consuming. There is an inversely proportional relationship between PADL and sedentariness, reduced autonomy, disability, risk of hospitalization, and death [51]. Besides, the disease severity (dyspnea levels, $\text{SpO}_2 < 88\%$, $\text{DLCO} < 40\%$, 6MWD, the extent of honeycombing on computed tomography, level of PH) was associated with lower physical activity among patients' stable IPF [52].

4.6.1 PADL assessment

PADL assessment is performed either by direct observation (time and staff consuming because it is individually applied), energy expenditure (for research

calorimetry), questionnaires, and other devices with motion sensors (detect movement and quantify PADL: pedometers, accelerometers, or physical activity monitors). The questionnaires are subjective methods of evaluating the effects of the symptoms on the patient's daily activities and quality of life, and they are instruments that are used in evaluating PRP [53]. Achieving progress through training programs can motivate the patient to pursue an active lifestyle for as long as possible. Pedometers measure only the distance covered daily (10,000 steps/day for a healthy lifestyle in the general population), but the effort intensity is better quantified by accelerometers [54]. These are preferred in sedentary or disabled patients, being more sensitive to the detection and description of movements. Daily activity can be quantified using the activity monitor for at least seven consecutive days from awakening to bed [2]. The intensity of physical activity is evaluated on a scale of 1–5, depending on the energy expenditure, expressed in the metabolic equivalent task (METs) [55].

4.6.2 The questionnaires used in PADL evaluation

The questionnaires used in PADL evaluation for IPF are easy to apply, cheap, self-administered, validated (internal consistency and test-retest reliability) and correlate with the estimated energy consumption by the methods mentioned above. The most commonly used questionnaires in clinical studies, which are extrapolated to IPF patients, are as follows:

4.6.2.1 Self-report 7-day short form International Physical Activity Questionnaire (IPAQ)

Self-report 7-day short form International Physical Activity Questionnaire (IPAQ) [2, 56] consists of nine items which evaluate the level of physical activity that is quantified in METs for the effort intensity: vigorous (8 METs), moderate (4 METs), walking (3.3 METs), and sitting times. The total score is the sum of all types of activities (the number of minutes spent/day) multiplied by the level of energy (MET) and multiplied by the amount of time spent/week [(MET)-min/week] [55]. An active patient is considered to perform 600 METs-min/week (150 min/week \times 4METs moderate intensity activity) [54, 57]. $\text{IPAQ} \leq 417$ (MET-min/week) $\Delta\text{SpO}_2 < 10$ (%) represents the cutoff which predicts mortality in patients with IPF [2]. However, there were differences between the self-reported patient score on the questionnaire and the accelerometer's results, depending on sex, age, education level, and body mass index (BMI). There is also a short form for this IPAQ [58].

4.6.2.2 Barthel index (BI)

Barthel index (BI) is based on basic physical activities for self-grooming, such as feeding, toilet use, bladder and bowel control, walking, dressing, bathing, brushing, or ascending and descending stairs. The total scores vary between 0 and 70; higher scores are associated with more active subjects. A change in the BI score after 1 month of ET4 was arbitrarily classified as mild (a decrease of <10 points), moderate (10–15 points), or severe (>15 points) [59]. This index reflects the independence levels in PADL in IPF patients.

4.6.2.3 Baecke questionnaire

In *Baecke questionnaire*, the score reflects the level of energy consumed performing professional activities, sports, and entertainment and is also adapted for the elderly, obese, and Parkinson's disease or cardiovascular patients [60].

4.6.2.4 Stanford Seven-Day Physical Activity and Stanford Usual Activity questionnaires

Stanford Seven-Day Physical Activity and Stanford Usual Activity questionnaires are applied during an interview. The first one relates to the time spent doing physical activities and sleeping for the past 7 days. The second focuses on moderate and intense activities in the last 3 months [61].

The PADL level is positively influenced by supervised PRP that lasts at least 7–8 weeks.

4.7 The quality of life questionnaire

The quality of life questionnaire has been developed and validated extrapolating those applied to COPD patients, given the lack of a specific disease-specific questionnaire for IPF [56].

4.7.1 St. George Respiratory Questionnaire (SGRQ)

St. George Respiratory Questionnaire and *St. George Respiratory Questionnaire IPF-specific version (SGRQ-I)* consist of 50 items referring to three categories: symptoms (8 items), activity (16 items), and impact (26 items) [36, 62, 63]. The total score varies from 0 to 100 points. Higher scores reveal a poorer health-related quality of life. SGRQ-I is reliable and comparable to the original SGRQ [64]. The SGRQ score was significantly correlated with FVC, FEV1 (%), 6MWD, and MRC. On the other hand, it did not show a significant correlation with DLCO or the level of desaturation at 6MWD, compared with CAT questionnaire [64].

4.7.2 Medical Outcomes Short-Form 36 (SF-36)

Medical Outcomes Short-Form 36 (SF-36) is a generic health-related quality of life questionnaire. It consists of eight multidimension items as general health, vitalities, physical functioning, physical role/problems, body pain, emotional roles/problems, social functioning, and mental health. Each of the dimensions is scored from 0 to 100. Higher scores indicate a better health-related quality of life [65].

4.7.3 Hospital Anxiety and Depression Scale (HADS)

The *Hospital Anxiety and Depression Scale (HADS)* can be applied in any disabling chronic disease which leads to impairment of the psychic/emotional status of patients [66].

4.7.4 The Chronic Respiratory Disease Questionnaire (CRDQ)

The *Chronic Respiratory Disease Questionnaire (CRDQ)* refers to dyspnea, fatigability, emotional impact, and self-control [67].

4.7.5 COPD assessment test (CAT)

COPD assessment test (CAT) was compared with other instruments applied to patients with IPF showing good psychometric properties among ILD patients. It is a self-administered questionnaire with eight items, each scored on a scale from 1 to 5. There is a strong correlation between the CAT score and SGRQ score, indicating that it can be used for health-related quality of life assessment among patients with

IPF. Furthermore, CAT showed higher correlations with the physiological parameters than the SGRQ [67].

4.7.6 Tool to Assess Quality of Life in Idiopathic Fibrosis (ATAQ-IPF)

The *Tool to Assess Quality of Life in Idiopathic Fibrosis (ATAQ-IPF)* is an extensive, 74 items, a disease-specific instrument which measures the symptoms adequately, sleep, emotions, relationships, therapies, finances, and many others. The score correlates with disease severity, but future studies are needed [8].

4.7.7 King's Brief Interstitial Lung Disease (K-BILD)

The *King's Brief Interstitial Lung Disease (K-BILD)* questionnaire is a validated and responsive questionnaire for longitudinal assessment of ILD patients' quality of life. A score change of 5 units is significant [68].

4.8 Muscle strength assessment

In muscle strength assessment, types of muscular impairment refer to mass (of different anatomical sites: biceps, triceps, etc.), strength, endurance, and performance [69]. Peripheral muscle force measurement may be important in PRP for understanding the impact of the disease on muscle mass, identifying patients at risk for physical impairment, and identifying those who can benefit from the prescription of an individualized resistance training program. Peripheral muscular dysfunction is a consequence of sedentary lifestyle, adopted by patients to avoid the symptoms and systemic effects of the disease (inflammation, hypoxemia, nutritional deficiency, corticosteroid side effects, electrolyte imbalances). Commonly, quadriceps muscle dysfunction is used for the assessment of peripheral muscle strength. The tests that are used may be volitional (volitional techniques: identification of the maximum weight that the patient can lift, manual muscle testing with MRC scale, or by dynamometers: handheld and computerized) or non-volitional (electrical stimulation of involuntary muscle contraction). The quadriceps maximal isometric voluntary contraction (QMVC) or predictive formulas (different equations for predicting quadriceps muscle strength) are described in literature, especially in studies on patients with COPD [70–72]. It is considered that patients have quadriceps muscle weakness if the value is <80% of predicted [73]. Knee extensor and elbow flexor strength could be measured with handheld dynamometer [69].

5. Correlation between exercise tolerance, daily physical activity, and survival rate

a. **6MWD** is an independent and discriminating predictor of mortality among patients with IPF, more accurate than FVC or DLCO [74, 75]:

- Basal value <250 m correlates with twofold increase in mortality, and if it is less than 207 m, patients have a more than fourfold greater mortality rate.
- A decrease of $SpO_2 < 88\%$ during 6MWT is marker for increased mortality.
- A decrease in the walking distance within 6 months, greater than 50 m, would increase the mortality rate by three times.

- A delayed heart rate return in 1 minute after the end of the 6MWD test and a variation <13 beats/min are strongly correlated with increased mortality.

b. Daily life physical activity level [76–78]:

- IPF patients are highly sedentary, having a daily physical activity level which is 35% lower than healthy sedentary controls.
- A value under 3.287 steps/day on accelerometers was associated with a poorer prognosis and three times higher risk for death for IPF patients.
- Peripheral muscle dysfunction related with a decrease of the physical activity level of daily life and exercise limitation is associated with reduced survival.

6. Types of pulmonary rehabilitation programs

PRP for IPF patients include several types of exercises, such as aerobic, resistance, flexibility, balance training, and respiration technique. Their selection is based on the everyday lifestyle of each patient, preferences, disease severity, and the advantages of where the PRP will take place:

- “Inpatient” rehabilitation centers are a more appropriate method for the supervised exercise programs taking into account the symptoms and the risk of severe effort desaturation that may occur. The advantage is that during exercise sessions, patients are monitored for blood pressure, heart rate, SpO_2 , and symptoms, and the urgent treatment is available in case of complications [79, 80].
- “Outpatient”-based programs take place in the patient’s home under the assistance of a healthcare professional with expertise in exercise training.
- *Home-based rehabilitation* programs are an alternative to in-/outpatient programs. They are easy to perform, practical, cheap, and equally as effective, but unfortunately have a lower adherence rate and less improvements, so it is necessary to be supervised by phone calls [12, 78, 79, 81].
- Combined programs start in a specialized structure and continues at home after the patients are familiar with the type and intensity of exercise [83].

PRP includes physical training, patient education, and nutritional and psychological support [11]. Regardless of the type of PRP, it is beneficial to start it as soon as possible. We will keep in mind that the intensity of rehabilitation depends on the severity of functional impairment and is personalized to each patient. The physical therapist starts from breath retraining and relaxing postures which increase chest expansion and relax the inspiratory muscles (Jacobson, Schultz technique). They reinforce proper breathing patterns (diaphragm) and include exercises that tonify respiratory and skeletal muscle (endurance and resistance) in order to increase patients’ exercise capacity [2].

7. Types of exercises

The main objective of these training programs is teaching patients how to perform a series of structured and repetitive exercises that improve or maintain their physical fitness and decrease the respiratory discomfort [82].

Educating patients about pursuing an active lifestyle even in the presence of IPF should be based on information about the types of exercises that can be performed, the regularity and duration of each session, and general instructions on how and what to follow through the program. During the follow-up with their patients, the doctor may be confronted with various questions, doubts, and anxiety from the patients. In the early stages of the disease, when the symptoms are not disabling, the patient's motivation to follow a PRP is low. In advanced stages, the motivation is stronger because dyspnea limits exercise capacity and daily activities. According to several studies, the PRP with greatest benefits have 6–12 weeks programs, with 2–3 sessions per week of 30 minutes duration. The exercise intensity is determined by patients' walking speed on 6MWD (starting at 70–80%), or by the maximum workload on cycle ergometer test (50–60% or more of peak WR on CPET for cycling), maximum heart rate (up to 80%), or on the intensity of symptoms on the Borg scale (to reach a score above 5–7). The effort intensity can also be calculated from an average heart rate \pm 5 beats, obtained in the last 3 minutes of the effort test [2, 21, 33, 84].

A comprehensive training program should include several types of exercises: breathing and balance exercises, aerobic, endurance, and flexibility (stretching) [2, 12, 20, 33, 84].

For increasing the endurance to effort, aerobic exercises can be used to train different muscle groups, depending on the patients' preferences and physical resources. Aerobic exercises can include walking, stair climbing, treadmill walking, leg cycling, semi-recumbent cycling, or step climbing on an ergometer adapted for lower limbs [16]. Resistance training refers to the increase in muscle strength and can be achieved by performing repeated exercises for upper and lower limbs, arm raising, knee-extension, sit-to-stand, and strength training using elastic bands. In these types of exercises, the muscles work against an external force applied by a device from the physiotherapy room or against their own body weight. They can also use weights. These exercises are grouped in 2–4 sets, with 10–15 repetitions, followed by breaks of 45–60 s. Each set of exercises targets specific muscle groups [85]. These exercises are recommended due to the fact that IPF patients have reduced muscle mass, strength, and endurance, compared with healthy subjects. They develop atrophy and muscle weakness, especially in lower limbs [86, 87]. Stretching exercises are activities designed to maintain or increase joint mobility and muscle relaxation. Strength training targets major muscle groups of the upper and lower body. There is a wide range of exercises that could be applied by physiotherapist [88]:

- Shoulder wheel
- Multiple movements of shoulder by changing his position as abduction, externally rotates the shoulder, flexion, and extension
- Sitting or standing biceps curls
- Mid-back rowing
- Shoulder flexion or extension
- Sitting or standing chest presses and triceps extensions
- Lower body exercises: standing hip abduction and extension
- Seated knee flexion and extension

- Internal and external rotations of the abducted shoulder with the elbow flexed 90 degrees
- Wall push-ups
- Chair squat
- Dumbbells shoulder press
- Dumbbells biceps curls
- Dumbbells arm extension
- Abdominal curl-ups
- Seated single leg hamstring stretch
- Standing quadriceps stretch
- Chest stretch
- Overhead reach stretch and wall cat stretch

For strength training there are three types of therapeutic bands that can be used: yellow, followed by red, and then green.

Respiratory muscle training or breathing exercises are extremely important, especially for patients with advanced disease, because they focus on diaphragm training, by teaching patients abdominal breathing techniques [79, 89].

There are no strictly standardized protocols for the PRP, allowing an experienced physiotherapist to tailor the patient's training structure in order to maximize the benefits.

The structure of a rehabilitation program should be seen as a multistage process:

- Firstly, the patient learns different types of exercise and different techniques, which can be divided into four categories (aerobic, endurance, flexibility, and breathing). Their intensity should be adapted to the severity of patient's pulmonary impairment, typically 50–60% of the work peak rate for aerobic exercise and 70–80% of the walking speed in 6MWT for endurance exercises (bicycle, treadmill, walking). The program can start with breathing exercises or balance training, continued by aerobic exercise and resistance training. Exercises should primarily focus on increasing the strength and the muscle mass of the lower limbs and diaphragm. The interval technique can also be used, allowing the patient to rest between exercises. In patients who experience desaturations ($\text{SpO}_2 < 85\%$) during training, oxygen supplementation should be considered in order to maintain SpO_2 above 88% [21]. During a program of 2–3 sessions/week, for 4–6 weeks, under the supervision of a physiotherapist, a patient can learn and become adequately trained to pass into the second phase.
- In the continuation and improvement phase, subjects can progressively increase both the frequency (3–4 times/week), duration, and intensity of the sessions. The aerobic program can be extended to 20–50 min and can be performed at an intensity of 60–85% of the work peak rate. The resistance

training can last between 20 and 30 min, with an intensity of 80–100% from the average walking speed obtained in the 6MWD test. Also, the programs recommend including 10–15 min of stretching and a minimum of 5 min of diaphragmatic or pursed lip breathing [90].

- The maintenance phase is important for preserving the benefits of a PRP, for decreasing the anxiety and depression level, and for increasing the quality of life. It is recommended to maintain the types and the intensity of exercises that will lead to a level of fatigue between 5 and 7 on the Borg scale.

Each patient should be reassessed at 3–6 months, in terms of effort tolerance, quality of life, disease progression, and response to pharmacological treatment. In brief, a supervised training program for patients with IPF should recommend:

- 4–6 weeks, 2–3 sessions/week
- Aerobic effort 20–40 min
- Stretching 10–15 min
- Breathing techniques 5–10 min
- Adjusting the work intensity so it can be tolerable for the patient
- Oxygen supplementation for patients who desaturate (SpO_2 85–88%)
- Intervals between exercises allowing better oxygenation
- Patient reassessment at the end of the 6 weeks

In a comprehensive PRP, patient's education begins from understanding the patient's needs and providing detailed information regarding the nature and expected course of the disease, solutions for symptoms management, benefits and side effects of treatments (depression, anxiety, obesity, diabetes, cardiovascular disease), the indication of oxygen supplementation, energy conservation techniques, relaxation and recreation methods, stress management, coping techniques for anxiety and depression, smoking cessation, and solutions for the improvement of quality of life. Medical education sessions usually precede exercise training sessions. This will be individualized for each patient, ensuring optimal communication between the patient and the multidisciplinary team. Educational assessment begins with the identification of difficulties, focusing on the change of the health-related behavior. Goals need to be established in the short, medium, and long term, to increase the patient's motivation to follow a PRP. Educational therapy plays a role in the relief of symptoms and quality of life improvement, optimizing the benefits of a PRP [11].

Nutritional support refers to weight control and a balanced diet, with obesity or weight loss being associated with a poor prognosis. Adipose mass can be evaluated pre- and post-PR, using different skinfold calipers for the analysis of body composition by skinfold thickness measurements [91].

Due to the life-threatening course of the disease, the psychological support should be considered for each patient. The dialog among the patient, the patient's family, and healthcare professionals can decrease the depression and anxiety in more than 50% of ILD patients [56].

8. Results of the exercise training programs

Studies conducted support the beneficial effects of PR programs, at the end of which patients with IPF present [15, 19, 33]:

- Improvement in functional capacity
- Improvement in 6MWD results over SMD: 35.63 m (95% CI 16.02–55.23 m)
- Improvement in $V'O_2$ peak at 6WMD 1.46 mL/kg/min⁻¹ (95% CI 0.54–2.39 mL/kg/min⁻¹)
- Increased physical activity levels (IPAQ)
- Significant reduction in dyspnea: SMD –0.68 (95% CI –1.12 to –0.25)
- Improvement in wellness and health-related quality of life, especially for those with severe disease SMD 0.59 (95% CI 0.14–1.03)
- Increased muscular fitness

Quality of the evidence regarding the impact of PR programs in IPF patients after Dowman et al. [15]:

1. Change in 6-min walk distance—moderate ⊕⊕⊕⊖
2. Change in $V'O_2$ peak uptake at cardiopulmonary exercise test—low ⊕⊕⊖⊖
3. Change in maximum ventilation cardiopulmonary exercise test—low ⊕⊕⊖⊖
4. Change in dyspnea score MMRC Dyspnea Scale—low ⊕⊕⊖⊖
5. Change in quality of life CRDQ (total score)—low ⊕⊕⊖⊖
6. Month survival—low ⊕⊕⊖⊖

A follow-up was performed 8–12 weeks after end of rehabilitation.

The review used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) to evaluate the study results: “Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate” [15].

The increase in effort capacity is directly related to training frequency, three to five sessions per week being optimal and fewer than two sessions being unlikely to produce meaningful change [92].

It is considered that a PR has been beneficial if there has been an increase of more than 50 m at 6MWD test (31–81 m gained in PR in different clinical trials) and a minimum amount of physical activity at 200 METS-min/week [10 min × 4METS (moderate intensity in the IPAQ questionnaire) × 5 times/week. Longer programs and more frequent sessions (12 or more) appear to have a greater benefit; however these benefits can be lost after 3–6 months, if the training does not continue and patients fail to maintain an active lifestyle [11]. There are discrepancies in the

outcome of the studies, in patients who have undergone a pulmonary rehabilitation program, discussing the responder or non-responder label depending on whether or not the walking distance of 6MWD or $\dot{V}'O_2$ has improved. Non-responders are considered patients whose result of 6MWT did not rise above or equal to 30 m after PR (30 m considered as MCID) [93]. Also, the responders had FEV1 and TLC raised after the rehabilitation program and significantly increased $\dot{V}'O_2$ peak, carbon dioxide output ($\dot{V}CO_2$), and minute ventilation (VE) in the 6MWT post-PR test, while non-responders showed greater desaturation during exercise [93].

The different results of the studies can be explained by:

- Training programs with differences in intensity, duration, and type of administration (inpatient/outpatient, supervised/unsupervised)
- Small numbers of participants
- Methodological limitation: methods of randomization (uncontrolled studies or nonrandomized, unblinded study)
- Limitations of retrospective studies
- Different control batches (other types of ILD, sham, etc.)
- Patients entering PR at different stages of severity
- Inclusion and exclusion criteria
- No follow-up data after exercise training
- Different outcomes

9. Lung transplant pre- and post-rehabilitation programs

Conforming to the International Society for Heart and Lung Transplantation (ISHLT), this pulmonary transplantation is performed for a variety of advanced lung diseases, IPF, together with COPD, being the most common indication. However, in posttransplant survival, IPF is associated with the worst prognosis. For patients with IPF, transplantation and supplemental oxygen were the only treatments strongly recommended by the latest ATS consensus document. A transplant discussion is recommended from the moment the positive diagnosis is confirmed due to low survival [94, 95].

Medical and surgical interventions in transplants have progressed in the last few years. All of these lead to a changing demographic of patients undergoing lung transplantation, including older subjects with multiple comorbidities, respiratory failure, and even those who require bridging to transplantation [95]. To ensure a high rate of posttransplant survival, both in the short and long term, these patients must be physically and psychologically trained for this complex process. PRP plays an essential role in pulmonary transplantation, both by optimizing physical function prior to surgical intervention and by facilitating posttransplant recovery. Although these PRP are mandatory in most transplant centers, to date there is no international pulmonary rehabilitation guideline for this patient category [95].

Physiotherapists working with lung transplant candidates and recipients need expertise both in general exercise training principles and in pre- and posttransplant

rehabilitation, complications, oxygen titration, and side effects of medications. They should be able to adapt exercise programs according to the lung function changes and according to episodic illnesses (exacerbation) [95, 96].

Prior to transplant, patients should attend PRP and benefit from exercise training, aerobic, resistance, and flexibility, with or without oxygen support, in the tolerance limit. In early posttransplant period, mobility is advised even in ICU and in acute hospitalization, for the progression to independent function (transfers, walking, self-care, climbing stairs). In the next phase (1–6 month), they should gradually perform balance training, aerobic, resistance, and flexibility exercises, as tolerated. Oxygen can be supplemented to support exercise. In the long term (>6 months), patients should be included in home and community PR programs for maintaining and improving the benefits of this intervention [96]. All these aspects are the premises for a better prognosis and lower costs for the healthcare system.

10. General recommendations

- A multidisciplinary team that includes a respiratory specialist and a clinical psychotherapist should manage and supervise the inclusion in a PR program of patients with IPF and the structure and monitoring of the patients' exercise training sessions.
- In patients with severe IPF, it is preferred that programs are held in the hospital. In case programs are held at patient's home, then high-intensity exercises that could lead to desaturation and worsening of symptoms should be avoided.
- For long-term benefits, three to five sessions per week for a minimum of 6 weeks are optimal, less than two sessions being unlikely to produce significant change [92].
- Initially, the interval training method is preferred, and in time, the duration of the exercises can be increased. A break and rest are mandatory when excessive fatigue and dyspnea appear [12].
- The overall load increases gradually according to patient's tolerance, the intensity of effort being adjusted to patients' fatigue tolerance.
- Additional oxygen can be used during exercise as it allows for an increased endurance and intensity of exercise levels [1].
- Factors such as self-motivation, fear of adverse events, or comprehension may affect the ability to tolerate exercise training.

11. Conclusions

The pulmonary rehabilitation has become a clear indication as a non-pharmacological therapy for patients diagnosed with IPF. The benefits of pulmonary rehabilitation programs are reduced respiratory symptoms, especially dyspnea, and increased exercise tolerance and level of physical activity. All these lead to a lower level of anxiety and depression and therefore increased quality of life. These benefits are sustained in short term, 3–6 months. They can be maintained for a longer period if the patient has a responsible behavior and an active lifestyle.

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