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Pulmonary rehabilitation in connective tissue disease-associated interstitial lung disease: A systematic review

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Abstract. *Background and aim:* Interstitial lung disease (ILD) is the major contributor to mortality in between chronic lung diseases. ILD originates from voluminous pathophysiological factors. One of the reasons is connective tissue diseases (CTD). According to experts, patients with CTD-ILD may have a stable disease activity and not need conventional treatment. Also, with pulmonary rehabilitation (PR), these patients may benefit from improving clinical outcomes and regression in mortality. However, the characteristics of these patients and whether they have stable disease activity in practice are not known. *Methods:* The systematic review was performed via the AI-powered tool with six databases to conduct literature research. The methodologic quality of the studies, risk of bias, and level of evidence were assessed. *Results*: According to the final four included studies PR benefit moderate levels of evidence for lung functions and diffusion capacity, functional capacity, quality of life, dyspnea severity, and fatigue level. However, there was limited evidence for respiratory, and peripheral muscle strength for CTD-ILD patients. *Conclusions*: The literature shows that the use of PR for CTD-ILDs wasn't widespread. Our findings suggest that PR can be used in CTD-ILDs to recover clinical parameters like, lung functions, quality of life, dyspnea severity, and fatigue level. More comprehensive studies should be conducted to reveal the effect of the PR in the evidence-based frame.

Key words: connective tissue disease, lung diseases, interstitial, therapeutics, pulmonary rehabilitation, pulmonary medicine, respiratory therapy

Introduction

More than one hundred eighty inflammatory lung disorders are called interstitial lung diseases (ILD) (1). ILD has been caused by exposure, disease associations, a specific pathology, or no existing concrete reason (1). Architectural distortions of the lungs lead to ruin in lung functions, dyspnea, decrease in carbon monoxide diffusion capacity (DLCO), progressive muscle weakness, exercise intolerance, and decline in quality of life (QoL) as well (2). Edema and infiltration of white blood cells impair the capillary construction. There might be decreases in alveolar blood flow and ventilation restriction. The disease activity of ILD is based on etiology. More than 200 separate disorders can give rise to ILD (3). Connective tissue diseases (CTD) can convert into ILD within time, as well. CTD-ILD-associated pulmonary fibrosis progresses in 40% of cases of rheumatoid arthritis-associated ILD (RA-ILD), 32% of systemic sclerosis (scleroderma)-associated ILD (SSc-ILD), 16% of polymyositis/dermatomyositis-associated ILD (PM/DM ILD), and 24% of Sjögren's syndrome-associated ILD (SS-ILD) (4). Disease concept, clinical course, treatment responses, and prognosis change according to the disease activity (5). Involvement of the lung becomes a major decisive contributor to the increase

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in mortality in CTD-ILD (6). ILD can be the only manifestation of a yet-to-be-diagnosed CTD (7). Pharmacological interventions include antifibrotic agents, glucocorticoids, calcineurin inhibitors, tumor necrosis factor inhibitors, intravenous immunoglobulin, plasma exchange, and referrals for stem cell and lung transplantation. For systemic autoimmune rheumatic diseases (SARD) associated with ILD patients, glucocorticoids have been conditionally recommended as a first-line ILD treatment. Nintedanib which is antifibrotic has been demonstrated to reduce the rate of forced vital capacity (FVC) decline in patients with SSc-ILD (scleroderma) (8). However, for SARD ILD other than SSc-ILD, the early use of Nintedanib is not currently advised (9). Besides conventional treatment, rheumatologic rehabilitation, physiotherapy, pulmonary rehabilitation, aerobic, resistance training, yoga, tai chi exercises, supplemental oxygen, and smoking cessation have been conditionally recommended according to the latest American College of Rheumatology (ACR) guideline for the treatment of ILD in people with SARDs (9,10). Interventions that target an increase in physical fitness and physical activity level are recommended to prevent cardiovascular disease risk in patients with inflammatory rheumatic diseases (11). Since obstructive pulmonary diseases have similar outcomes to ILD, PR has been used in ILD in the distant past to increase QoL, physical fitness, well-being, participation in activities of daily living (ADL), and struggling with dyspnea (12,13). PR covers resistance and supervised specified aerobic exercises, for CTD-ILD patients (14). Nonetheless, the optimal delivery prescription of PR for CTD-ILD has not been agreed upon, like in ILD (15,16). Recently, there have been an increasing number of studies that investigated more specifically autoimmune diseases related to ILD (17), despite more difficult access to PR of all ILD patients (18). Therefore, this systematic review aims to demonstrate the effectiveness and safety of PR in CTD-ILD patients on clinical outcomes.

Methods

Data sources and searches

Current review was performed to investigate the efficacy of PR in CTD-ILD patients. The study protocol registry was taken from the International Prospective Register of Systematic Reviews (PROSPERO ID CRD42023442754). Data were collected with MESH search terms' lung Diseases, Interstitial', 'Rheumatic Diseases' 'Therapeutics', and 'Pulmonary Medicine' from PubMed, Scholar, Cochrane, Web of Science, PEDro, and SCOPUS databases with Boolean logic between inception through July 2023 (Table 1). Data collection is shown below (Figure 1). All 2835 results were collected into the Mendeley Reference Manager program file and transferred to the Rayyan AI-Powered Tool (19). 704 duplicated studies were determined via Rayyan and eliminated.

Study selection

The selection was identified by the PICO framework in Table 2. The main inclusion criteria were based on investigating the efficacy and prognostic effect of PR in CTD-ILD and healthy controls. Cross-over, randomized, and non-randomized controlled studies were included. Participants in included studies according to differential diagnostic criteria (e.g. the relative decrease in FEV1- at least 10% and in DLCO ≥ or <40%, fibrosis in computed tomography scan, confirmed diagnosis of CTD by a rheumatologist which was met ACR/ European League Against Rheumatism criteria or serology results) were accepted (20-22). Studies that investigated the effect of PR on lung function, respiratory muscle strength and endurance, DLCO, QoL, exercise capacity, and adverse events as main outcomes were comprised. Studies that include CTD-ILD patients were designated as a main group. Other ILD etiologies such as IPF and asbestosis were defined as internal controls. Case reports, case-control, cohort, congress abstracts, trial protocols), animal studies, editorial letters, systematic reviews meta-analyses, and the existence of severe comorbid neurologic, and orthopedic illnesses were excluded. Studies were first screened by title and abstract. The results from database research were assessed independently in a blinded study design by two researchers (AD and IS). The agreement rate between authors on study exclusion was 99.7%. Resolvement of conflicts was made in the common meeting.

Data extraction and quality assessment

AD and IS demonstrated included studies according to an author name, year of publication,

Table 1. Summary of the search strategy via MESH terms.

Mesh Terms	Search Terms
Lung Diseases, Interstitial	"Lung Diseases, Interstitial" [Mesh] OR "Diffuse Parenchymal Lung Disease" OR "Interstitial Lung Diseases" OR "Diffuse Parenchymal Lung Diseases" OR "Interstitial Lung Disease" OR "Lung Disease, Interstitial" OR "Pneumonia, Interstitial" OR "Interstitial Pneumonia" OR "Interstitial Pneumonias" OR "Pneumonias, Interstitial" OR "Pneumonitis, Interstitial" OR "Interstitial Pneumonitides" OR "Interstitial Pneumonitis" OR "Pneumonitides, Interstitial"
Rheumatic Diseases	"Rheumatic Diseases" [Mesh] OR "Disease, Rheumatic" OR "Diseases, Rheumatic" OR "Rheumatic Disease" OR "Rheumatism"
Therapeutics	"Therapeutics" [Mesh] OR "Therapeutic" OR "Therapy" OR "Therapies" OR "Treatment" OR "Treatments"
Pulmonary Medicine	"Pulmonary Medicine" [Mesh] OR "Respiratory Medicine" OR "Medicine, Respiratory" OR "Medicine, Pulmonary" OR "Pulmonology" OR "Pneumology" OR "Pneumonology"
Undifferentiated Connective Tissue Diseases	"Undifferentiated Connective Tissue Disease"

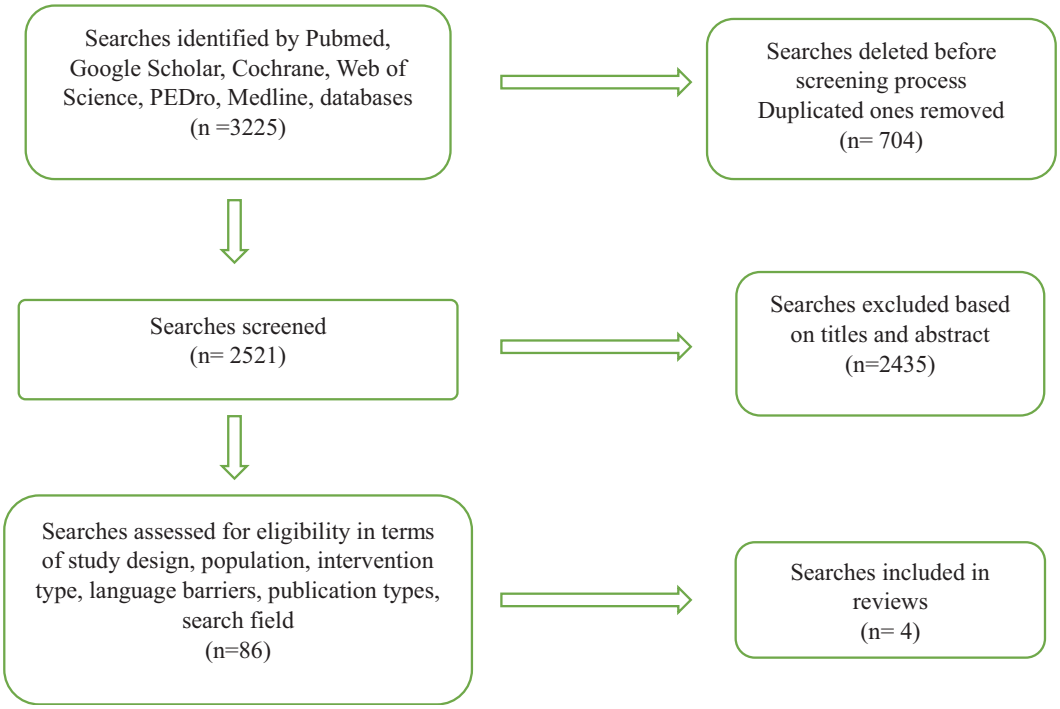

Figure 1. Flow chart of the systematic review.

country, study design, participation characteristics mean age of participants, intervention training parameters, intervention duration, control training parameters, outcomes, and results.

To decide the level of evidence of each study, the *EBRO* (Dutch Evidence-based Richtlijn Ontwikkeling Guideline Development and *Modified Bakker Scale* was used (23,24). There are 5 levels in EBRO which are A1, A2, B, C, and D. Results were classified with the primary outcome by EBRO. The Modified Bakker Scale was used to classify the level of evidence into *strong, moderate, limited, conflicting*, or *weak*. The decision to categorize the level of evidence was made based on methodologic quality and consistency (24). The methodological quality of included studies: AD and IS assessed the quality and risk of bias (RoB) in a blind study design with the PEDro scale. It investigates the internal and external validity that covers the generalizability and applicability of the trial (25). Controlling Risk of Bias of Included Studies: The

Table 2. PICOS evaluation of the study.

Parameters	Inclusion Criteria	Exclusion Criteria
Participants	Patients with ILD with rheumatological diseases	Abstracts, case reports, case series, editorials, letters, and opinion pieces. Participants who have severe comorbid neurologic, and orthopedic illnesses
Intervention	Studies in which pulmonary rehabilitation was compared with no pulmonary rehabilitation or with other therapy in people with ILD.	
Comparator	Pulmonary treatments, and pulmonary rehabilitation programs which are guided by ATS/ERS	Usual care (regular medical care alone)
Outcomes	Safety Health care utilization Lung function Respiratory muscle strength and endurance Diffusion capacity Quality of life Exercise capacity Adverse events	Studies without any defined clinical outcomes
Study Design	Cross-over, Randomized controlled studies, non-Randomized controlled studies	Case report, case-control, cohort, unpublished studies (e.g. Conference abstracts, trial protocols), animal studies, editorials, correspondence letters reviews, meta-analyses, systematic reviews, non-English studies

revised version of the Cochrane RoB tool for RCTs (RoB-2) and the ROBINS-I tool for n-RCT was used (26). Results were explained as low, high, and unclear in the RoB-2 tool. The possible answers are low, moderate, serious, critical risk of bias, and no information in the ROBINS-I tool (27).

Results

Data collection results and study characteristics

The total extracted articles were 3225. The publication years of the studies are between 2009 and 2022. Duplicated 704 articles were deleted. Therefore 2521 articles were first screened. According to the EBRO checklist, 86 articles were chosen as eligible. They were assessed in abstract and title form and labeled as include, exclude, or maybe. In conclusion, 4 articles were analyzed for review, which were 2 RCTs, 1 n-RCT, and 1 quasi-experimental studies. The trial's methodological quality ranged from 1 to 10 points based on the PEDro scale. Although PR isn't widespread in this population, its benefit has been demonstrated in current findings. The average methodological quality score was 6.25 points, which is accepted as a '*good*' result (28,31). Table 3 shows the characteristics of the studies. The most common flaws in the studies were the blinding and the existence of a control group. Seventy-four of the total 221 participants were male, 111 of them were female and 36 participants' gender wasn't indicated. Aerobic and resistance training for 68 patients with IPF, asbestosis, and CTD-ILD (28) aerobic, resistance, flexibility, and postural control training for 9 scleroderma-related ILD patients (29); aerobic, resistance, and motor function training which was therapist-oriented home exercise (TOHR) for 16 Ssc with ILD patients (30); breathing, resistance and aerobic exercises for 37 Ssc with ILD patients were investigated (31). Seventy patients took medical treatment synchronously during study process. For Dowman et. al. 's study, thirty-five patients (47.2% of the exercise training group) took medical treatment (respectively, 25 patients had prednisolone, 8 patients had immunosuppressant, and 1 patient had pirfenidone). Also, 20 patients of 23 CTD-ILD population used prednisolone and immunosuppressants (28). Among 16 SSc cases, seven cases were treated with low-dose corticosteroids (prednisone 4–10 mg/day) also two of them were simultaneously receiving oral azathioprine during the study. Moreover, 14 people had infusive therapy with iloprost in the control group of Antonioli et. al.'s study (30). Details of pharmacological treatment weren't featured in Gomes De Alegria et. al and Yakut et. al.'s studies. There was no notable difference

Table 3. Characteristics of included studies.

Author name, year of publication country	Study design	Sample characteristics	Intervention training parameters	Intervention duration	Control training parameters	Outcomes	Result	Level of evidence
Dowman et al. 2017 (*28*) (Australia)	RCT, multicenter randomized, assessor-blinded	n=142 ILD (**61 IPF+ 22 asbestosis+ 23 CTD-ILD+ 36 ILD with other etiologies**) IPF group: men=41; women=20 Asbestosis group: men=22; Women=0 CTD-ILD group: men=4, Women= 19 There is no information about men/women ratios in ILD with other etiologies, TLCO (%pred) <55% in all groups FVC (%pred) <80% in IPF, <86%in asbestosis, <79% in CTD-ILD TLC (%pred) is lower in IPF than in CTD-ILD and most in the asbestosis group.	Aerobic and resistance exercises: **n=74** **Aerobic exercise:** with treadmill: %80 of peak walking speed; with cycling: %70 of max. work rate by 6MWT result, twice a week **Resistance training:** 20 rep ULRT+ LLRT, 10-12 RM RPE of 12-14/6-10 on Borg scale, twice a week **Home exercise, patient education session Pharmacological intervention:** Prednisolone, n=25/ Immunosuppressant, n=8/ Pirfenidone, n=1/ N-Acetylcysteine, n=0/ Nintedanib, n=0) Totally 30m.	8 weeks	Usual medical care: **n=68** (Prednisolone, n=22/ Immunosuppressant, n=6/ Pirfenidone, n=1/ N-Acetylcysteine, n=2/Nintedanib, n=0) Patient education sessions and once-a-week telephone call	**6MWD (primary outcome),** muscle strength via hand-held dynamometry, HRQoL via CRDQ and SGRQ-I, dyspnea via UCSD SOBQ and mMRC, anxiety and depression level via HADS, global rating of change Lung functions, TLCO, lung volume, and PASP were assessed in the pre-intervention. (9. Week and 6. The month were the assessment dates.) At 9. Week n=135 At 6. Month n=126	**improvement:** p<0.05 6MWD (asbestosis>IPF> CTD-ILD) HrQoL at only 9. weeks (except SGRQ-I domain) **No effect:** p>0.05 Dyspnea Knee extensor muscle strength Elbow flexor muscle strength **Decreased** 6MWD achievement between IG-CG declined at 6. month from 25m. to 21 m. (p<0.03) Rise in HrQoL after exercise declined at 6. Month. (p<0.05) Succession in dyspnea management was affected at 6. Month negatively. (p<0.06) Sustainment is important*. **MCID** Baseline 6MWD threshold of 477 m above which exercise training was less likely to achieve 6MWD improvements. For every 10m increase in baseline 6MWD, the gain in 6MWD at 9 weeks declined by 1.4 m.	B

Table 3 (*Continued*)

Author name, year of publication country	Study design	Sample characteristics	Intervention training parameters	Intervention duration	Control training parameters	Outcomes	Result	Level of evidence
Gomes de Alegria et al. 2022 (*29*) (Brazil)	Quasi-experimental, pre-post design	n=12 scleroderma with associated ILD women patients, Limited cutaneous scleroderma, n=7, Diffuse cutaneous scleroderma, n=5 anti–topo I positivity, n=8 Anti-RNAP III positivity, n=3 Anti-centromere positivity, n=1 Normal spirometric pattern, n=5 Restrictive spirometric pattern, n=7	**TOHR: aerobic resistance+flexibility+postural control exercises:** n=9 Totally 60 m, 3 times a week **muscle strengthening** via resistive exercises (light free weights) **aerobic resistance exercises** via functional movements (no advanced information) **flexibility exercises** via calisthenic exercises **postural control training** via proprioceptive exercises intensity <4 borg scale, SaO2> %92	12 weeks	-	SAD and ILD degree via lung ultrasound, Lung function means impact on the respiratory system via impulse oscillometer n=9 (pre/post-intervention evaluation)	**Improvement:** Resistive and reactive parameters were improved after 12 weeks of TOHR($p<0.05$). There was an improvement in SAD post-TOHR($P<0.05$). **No effect:** TOHR didn't cause any significant ultrasonic changes. **Decreased:** FVC was decreased between pre/post TOHR ($p=0.06$). **MCID** According to the impulse oscillometer results, small airway disease may indicate prominent bronchiolar involvement in scleroderma with associated ILD. B-lines>2(an indicator of increased density of the peripheral lung parenchyma) existed between pre/post TOHR($p=0.07$).	B
Antonioli et al. 2009 (*30*) (Italy)	n-RCT	N=90 (initial) systemic sclerosis patients with ILD IG: women=16, men=0 CG: women=16 men=1 mean disease duration (years), IG: 14.5 CG:9 DLCO, IG: 111% CG: 93% FVC, IG: 70% CG: 59% Serology positivity results, IG: ANA: 16/16 ACA: 6/16 Anti-Topo I: 6/16 CG: ANA: 17/17 Aca: 6/17 Anti-Topo I: 5/17 ILD prevalence in IG n=7 in CG n=9	**Respiratory exercises+ motor function training,** n=16 via treadmill and free walking for LE, OT, and finger stretching exercises **TENS, magnetic field therapy laser therapy, radar therapy, ESWT** n=7 **Ultrasound therapy**, n=8 + **the home exercise program** was given if the session was terminated total 30 m and 10 sessions **Usual medical care,** n=12, Low-dose corticosteroids (prednisone 4-10 mg/day), n=7/ **azathioprine, n_2 (synchronously with study process**/ cyclophosphamide, n=3	2 weeks	-	Hand mobility via hand mobility test, HrQoL with SGRQ and SF-36 questionnaires, skin thickness via modified Rodnan Skin thickness Score, lung function with spirometry, exercise capacity with 6MWD, general health level via Health Assessment Questionnaire Disability Index (HAQ-DI) T0(at the end of last week)-T2-T4 (starting point-2. Month- 4. Month)	**Improvement** There was an improvement in general health and physical functioning parts of SF-36 between T0-T4($P<0.05$). HrQoL was improved between T0-T4 ($p<0.05$). Hand mobility was improved after intervention ($p<0.05$). There was an improvement in any of the outcome measures in CG between T0 and T4 ($p>0.05$). **No effect** 6MWD didn't change between T0 and T4. **Decreased** HAQ-DI was progressively decreased within the 4. month-time period ($p>0.05$). **MCID** In Ssc with ILD patients, HAQ-D MCID is 0.14, in SGRQ MCID is -0.4%.	B

Author name, year of publication country	Study design	Sample characteristics	Intervention training parameters	Intervention duration	Control training parameters	Outcomes	Result	Level of evidence
Yakut et al. 2021 (*31*) (Turkey)	RCT, randomized block design, blind randomization research,	n=37 systemic sclerosis patients with pulmonary involvement in Supervised-EG women= 16; men=3 in Home-EG women=15; men=3 BMI in SEG: 24.85 ± 3.20 in HEG: 26.31 ± 5.59 Limited Ssc, disease type, in SEG: 15 in HEG:16 Diffuse Ssc, disease type, in SEG:4 in HEG:2	***Supervised exercise group (SEG)*** **Breathing exercises** with pursed lip breathing, thoracic expansion exercises, diaphragmatic breathing exercises 5-10 reps/1 set/10 m **Resistance exercises**(for scapular adduction, bilateral shoulder flexion-hyperextension abduction, knee extension, hip flexion, with 4-way straight leg raises, squats, plunk, sit-ups, 50%-80% of 1 RM and 3-6 according to Borg scale 8-12 repetitions/1 set/ 15-20 m. **Aerobic exercises** with treadmill and cycling, 30 m, intensity at 40%-85% of heart rate reserve, 3-6 acc. to RPE) ***Home Exercise Group (HEG)*** **Breathing, posture exercises** as bilateral shoulder flexion-abduction-circumduction, trunk rotation, knee extension 4-way straight leg exercises, 1 set, 8- 12 reps) **Aerobic exercises** walking (20 m, at submaximal intensity 3-6 acc. To RPE) telephone calls with 2-week intervals (for both groups) total 1 hour, 24 sessions	12 weeks	-	Functional capacity (primary outcome) via 6MWT, pulmonary function via spirometer, diffusion capacity via single breath holding method technique, respiratory muscle strength via Mouth pressure measurement, dyspnea via mMRC peripheral muscle strength via hand-held dynamometry HRQoL via (HAQ-DI), (SHAQ, SF-36), fatigue level via Fatigue Impact Scale (FIS) baseline and post-intervention assessments	**Improvement** 6MWD and expected percentage value were improved in both groups ($p<0.01$) Pulmonary functions were significantly increased in both groups, except FEV1/FVC. There were non-significant improvements in lung functions in HEG. SEG made a more effective 6MWD change than HEG ($p<0.01$). Changes in MIP% and MEP% were significant in SEG, but only MEP% change was significant in HEG. Knee extensor strength significantly changed in both groups. Hand grip strength significantly changed in just SEG. The SF-36 PCS and SF-36 MCS increased in both groups. **No effect** - **Decreased** mMRC score was decreased in SEG after exercise treatment, but not in HEG. This means supervised exercise is more effective in decreasing dyspnea. HAQ-DI score decreased in both groups after exercise. After the exercise programs, significant decreases were observed in the digestive problems, respiratory problems, general disease severity domains, and total score of SHAQ in both groups. In both groups, the highest fatigue level decrease existed in the psychosocial part **MCID** The change in 6MWT in both groups was greater than the minimal clinical significance value indicated in respiratory diseases with obstructive and restrictive diseases.	A2

Abbreviations: IPF: idiopathic pulmonary fibrosis, ULRT: upper limb resistance training, LLRT: lower limb resistance training, RM: repetition maximum, RPE: rate of perceived exertion, 6MWT: 6-minute walking test, IG: intervention group, CG: control group, SGRQ-I: St George Respiratory Questionnaire IPF-specific version, PASP: echocardiographic assessment of pulmonary artery systolic pressure, MCID: minimal clinically important difference, TOHR: therapist oriented home rehabilitation, LE: lower extremity, OT: occupational therapy, TENS: transcutaneous electrical nerve stimulation, ESWT: extracorporeal shock wave therapy, HAQ-DI: Health Assessment Questionnaire-Disability Index, SF-36:Short Form 36 index, PCS: Physical Component Score, MCS: mental component score, TLCO: carbon monoxide transfer factor.

between usual care and exercise groups in terms of baseline pulmonary function, diffusion capacity, respiratory muscle strength, dyspnea severity, functional capacity, peripheral muscle strength, HrQoL, and fatigue levels for Yakut et. al.'s study. The intervention and control groups showed no baseline differences in the overall ILD population except for HrQoL and use of exertional oxygen, or across subgroups, except for MMRC dyspnea for Dowman et. al. 's study ($p > .05$). Table 4 summarizes of findings of PR on clinical outcomes in patients with CTD-ILD.

Controlling Risk of Bias of included studies Results and decision to level of evidence

The methodological quality of the studies was 6.25±3.86 points (between 1 and 10 points) (Table 5).

Three studies (28,30,31) had high quality (PEDro score≥6). Dowman et. al. didn't involve a blind therapist. Gomes De Alegria et. al. had the lowest quality level which was just enough to meet the eligibility criteria. Blinding, randomization, and allocation concealment were missing in Antonioli et. al.'s study. RoB 2 tool rated n-RCTs as "*low*" or *"some concerns*", due to the missing blinding (28,31) (Table 6).

RCTs had a moderate bias related to outcome assessment and reported results (29,30) (Table 7).

According to the EBRO checklist, 3 studies (28-30) were at the B level, due to the inadequate controlling of confounding factors, the existence of reference tests, and the control group. Yakut et. al.'s study was at the A2 level, with an appropriate study design (31).

Effect of different PR programs on outcomes

Effect of PR on lung function and diffusion capacity

Dowman et. al. found that the change between pre/post-intervention and at the sixth month decreased ($p>0.05$) in all ILD groups (n=142), except asbestosis and CTD-ILD groups in terms of FVC% predicted (pred.) and TLCO% pred. Total lung capacity wasn't reported in post-intervention (28). According to Gomes de Alegria et al., non-significant decreases in lung function were seen in scleroderma-related ILD. *An impulse oscillometer* was preferred to evaluate airway resistance and reactance. There was a significant increase in the airway's inertial properties and the lung periphery's capacitance after TOHR (29). Antonioli et. al. showed that there was no long-term effect (in the second and fourth month in post-post-intervention term) of exercise training (30). Yakut et. al. showed that after 12 weeks of supervised exercise, lung functions, and dyspnea severity improved in Ssc with ILD patients ($p<0.05$). There were improvements in the home exercise group, as well (31). The level of evidence was *moderate in SSc* (Tables 3 and 4).

Effect of PR on respiratory- peripheral muscle strength

Dowman et. al showed that 8-week aerobic, resistance exercises weren't sufficient to increase peripheral muscle strength in CTD-ILD (28). On the other hand, Yakut et. al. revealed that knee extensor and handgrip strength increased after supervised exercise ($p<0.05$). In the home exercise group, peripheral muscle strength was not affected except for knee extensor strength ($p>0.05$) (31). Dowman et. al. revealed an increase in respiratory muscle strength in the post-intervention term (28). Yakut et. al. showed an increase after supervised exercise as well. However, in the home exercise group, there is no significant in inspiratory muscle pressure ($p>0.05$) (31). Gomes de Alegria and Antonioli et. al. didn't investigate the change in muscle strength as an outcome of an exercise program (29,30). The level of evidence of muscle strength outcome measurement was *limited* in Ssc with ILD patients (Tables 3 and 4).

Effect of PR on functional capacity

Dowman et. al. showed that 6-minute walking distance (6MWD) improved after exercise training 6 months in CTD-ILD, but not in IPF or asbestosis patients. Participants who completed the program and were able to progress their protocol showed a greater increase in 6MWD[32]. Gomes de Alegria et. al. didn't investigate the functional capacity 29). According to Antonioli et. al., there was no sustainment in the post-intervention term ($p>0.05$) Yakut et. al. showed an increase in 6MWD in all Ssc-associated ILD patients. There was a significant difference in the restoration of functional capacity in favor of supervised exercise from pre to post-intervention ($p<0.05$) (31). The level of evidence was *moderate* in

Table 4. Summarize of findings of PR on clinical outcomes

Clinical Outcomes	What was found in Dowman et al.'s study (28)?	What was found in Gomes de Alegria et al. 's study (29)?	What was found in Antonioli et al. 's study (30)?	What was found in Yakut et al. 's study (31)?	Level of evidence
Lung function and diffusion capacity	-	**Improvement,** Resistive and reactive parameters of the lung were improved after exercise training (p<0.05). **Decreased,** FVC was decreased between pre/post-exercise training (p=0.06).	-	**improvement** Pulmonary functions were significantly increased in both groups, except FEV1/FVC.	Moderate evidence
Respiratory-peripheral Muscle Strength	**No effect,** in terms of knee extensor muscle strength, elbow flexor muscle strength (p>0.05).	-	-	**Improvement,** Changes in MIP% and MEP% were significant in SEG, but only MEP% change was significant in HEG. Knee extensor strength significantly changed in both groups. Hand grip strength significantly changed in just SEG. (p<0.05)	Limited evidence
Functional Capacity	**improvement** (p<0.05) **Decreased,** 6MWD achievement between IG-CG declined at 6. month from 25m. to 21 m. (p<0.03).	-	**No effect,** 6MWD didn't change between the post-exercise term and after 4 months (p>0.05)	**Improvement,** (p<0.01), in terms of 6MWD	Moderate evidence
Quality of Life	**Improvement,** (p<0.05) HrQoL at only 9. weeks (except SGRQ-I domain). **Decreased,** Rise in HrQoL after exercise declined at 6. Month. (p<0.05).	-	**Improvement,** sustainable between the post-exercise term and after 4 months (p<0.05).	**Improvement** p<0.05	Moderate evidence
Dyspnea Severity	**No effect** (p>0.05) **Decreased,** Succession in dyspnea management was affected at 6. Month negatively (p<0.06).	-	-	**Decreased,** mMRC score was decreased in SEG after exercise treatment, but not in HEG. This means supervised exercise is more effective in decreasing dyspnea.	Moderate evidence
Anxiety-Depression Level	**No effect** Between pre/ post-intervention	-	-	-	Limited evidence
Fatigue Level	-	-	-	**Decreased** In both groups, the highest fatigue level decrease existed in the psychosocial part	Moderate evidence
Hand Mobility and Skin Thickness	-	-	**Improvement,** (p<0.05)	-	conflicting evidence

Abbreviations: SEG: supervised exercise group, HEG: home exercise group, 6MWT: 6-minute walking test, HrQoL: health-related quality of life, SGRQ-I: Saint George Respiratory Questionnaire IPF- specific version, IG: intervention group, CG: control group, FVC: forced vital capacity, MIP: mean inspiratory pressure, MEP: mean expiratory pressure, FEV1: The forced expiratory volume in 1 second.

Table 5. Results of Methodologic Quality Assessment via PEDro Scale.

Article	Eligibility criteria	Random allocation	Concealed allocation	Similarity of groups at baseline	Blind subject	Blind therapist	Blind assessor	Adequate follow-up	Intention to treat analysis	Between-group analysis	Point estimates and variability	Total Score
Dowman et al. 2017 (28)						■						**10**
Gomes de Alegria et al. 2022) (29)		■	■	■	■	■	■	■	■	■	■	**1**
Antonioli et al. 2009 (30)		■	■		■	■						**6**
Yakut et al. 2021 (31)					■	■						**8**

White box: criteria met; black box: criteria not met.

Table 6. Risk of bias assessment of included RCT studies via Adapted Cochrane collaboration's Tool, RoB 2

Article	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dowman et al. 2017 (28)							
Yakut et al. 2021 (31)							

Black box: high risk of bias; grey box: unclear risk of bias; white box: low risk of bias

Table 7. The Risk of Bias assessment in Non-randomized Studies – of Interventions (ROBINS-I) assessment tool.

Article	*Bias due to confounding*	*Bias in the selection of participants for the study*	*Bias in the classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurements of outcomes*	*Overall bias*
Antonioli et al. 2009 (30)	+	+	+	+	+	-	-
Gomes de alegria et al. 2022 (29)	+	?	+	+	+	-	-

[a:] + = low risk of bias, - = moderate risk of bias, / = serious risk of bias, x = critical risk of bias, ? = no information

Ssc-associated ILD and CTD-ILD patients (Table 3 and 4).

Effect of PR on QoL

Dowman et. al. demonstrated significant improvements in QoL between pre/post-intervention. Improvement in QoL was lost in the sixth month of post-intervention in the exercise group QoL improved significantly in the asbestosis and CTD-ILD group (28). Gomes de Alegria et. al. didn't investigate the change in QoL (29). Antonioli et. al. found improvements in QoL in the post-intervention term, as well. There were 60%, 67%, and 47% increases in the "activity," "symptoms," and "impact" scores of the QoL scale, respectively were minimally clinically important differences after the exercise program in Ssc (30). Yakut et. al. demonstrated improvements in QoL in both groups with 0.123 points decrease in QoL scales as MCID for Ssc with ILD patients ($p<0.05$). Also, an increase in physical and mental components above the minimal important difference (respectively 2.25 and 0.18 points) for patients with SSc after exercise was found (31). The evidence level of QoL was *moderate* in CTD-ILD (Tables 3 and 4).

Effect of PR on dyspnea severity

Dowman et. al. showed the largest change in dyspnea was seen in the asbestosis group. They didn't detect changes following the exercise in CTD-ILD (28). Gomes De Alegria and Antonioli et. al. didn't investigate the change in dyspnea (29,30). Yakut et. al. found a decrease in dyspnea severity in the supervised exercise group ($p<0.05$). However, no significant differences were seen in the home exercise group ($p>0.05$) (31). The evidence level for dyspnea was *moderate* in Ssc-associated ILD patients (Tables 3 and 4).

Effect of PR on anxiety and depression level

Dowman et. al. found no difference between pre/post-intervention ($p>0.05$) (28). The level of evidence was *limited* in the CTD-ILD group (Tables 3 and 4).

Effect of PR on fatigue level

Yakut et. al found a decrease in fatigue perception in pre/post-intervention terms, especially in the supervised exercise Ssc-associated ILD group (31).

The evidence level for fatigue was *moderate* in Ssc-associated ILD patients (Tables 3 and 4).

Effect of PR on issues related to rheumatologic involvement (hand mobility and skin thickness)

Antonioli et. al. stated an increase in right-hand mobility in the post-intervention term(p=0.005). However, due to missing pre-intervention data, improvement wasn't estimated. For the left hand, hand mobility improved after exercise, as well. There was no difference in skin thickness between pre/post-intervention terms (p>0.05) (30). The evidence level for hand mobility was conflicting in CTD-ILD because the study had inconsistent findings (Tables 3 and 4).

Effect of pharmacological treatments on outcomes of PR

Dowman et al. found no influence of pharmacological interventions on anxiety and depression in the usual care group of CTD-ILD patients (p>0.05). Six CTD-ILD patients completed the exercise program, whereas five didn't. The factor associated with improved lung function and functional capacity in the CTD-ILD population is unknown, as the onset of PR and pharmacological treatment was unknown. In terms of change in 6MWT-d, usual care and exercise training groups of the CTD-ILD population they had an advantage in the sustainability of improvement in functional capacity. Between 9 weeks and 6 months, there was a non-significant decrease of 6MWT-d in the exercise group of the CTD-ILD population, unlike IPF and asbestosis populations (28). Because of no apparent distinction between the pharmacological treatment group and the rehabilitation group, the effect of pharmacological treatment on clinical outcomes wasn't presented in Antonioli et. al.'s study (30) (Table 3).

The evidence level for pharmacological treatments on outcomes of PR was *moderate* in CTD-ILD and SSc (Tables 3 and 4).

Discussion

The current study found that PR benefits lung functions, DLCO, functional capacity, QoL, dyspnea severity, and fatigue perception with moderate levels; respiratory and peripheral muscle strength, cross-sectional area of the lung with limited evidence; to hand mobility and skin thickness with conflicting evidence level in patients with CTD- ILD. There might be underlying other factors that stabilize or improve clinical outcomes for CTD-ILD. Despite recent advances in diagnosis and conventional therapy, patients with CTD-ILD mostly experience a chronic progression of the disease, leading to a growing accumulation of organ damage and disability. People with CTD-ILD experienced significant clinical improvements with PR following pharmacological treatment and disease severity is a predictor of long-term benefits, with milder cases showing more sustained treatment effects. Another important finding was that adhering to exercise progression and pharmacological treatment enhances these benefits to the fullest. Besides gold standard conventional treatment, PR has been suggested in CTD-ILD to prevent the progression of the disease (33). Aerobic, resistance, breathing, flexibility, postural control, and motor function exercises were used as PR modalities in studies that made up the current review (28,31). Only one study preferred occupational therapy and finger stretching exercises due to the involvement of upper extremity joints (30). Behavioral and environmental modifications such as exercise training, and smoking cessation, should be done before conventional treatment (34) with current findings (32). PR has been recommended in patients with obstructive pulmonary diseases who have common symptoms with ILD such as the existence of respiratory distress, hypoxemia, skeletal muscle dysfunction, increased respiratory effort, distorted airflow, ventilatory limitation, deterioration in QoL and exercise capacity (35,36). In terms of this current systematic review, baseline dyspnea was higher in the CTD-ILD group, rather than in IPF and asbestosis groups (28). Also, low FVC % existed (80% and above), despite having a normal range of carbon monoxide transfer factor % predictive in the CTD- ILD group (32). There were improvements in lung functions and DLCO after PR in CTD-ILD, like improvements in other ILD patients in previous reports (37). There are no studies investigating the effect of PR on pulmonary functions in CTD-ILD different phenotypes except for the included studies. Yakut et. al. showed that if supervised, combined exercise programs such as breathing, aerobic, resistive exercises, and self-management strategies are used, the possibility of

effect may increase in scleroderma-associated ILD (31). In contrast to Yakut et. al., Gomes De Alegria et. al found no improvement in lung functions after PR for the same population (29). Previous studies reported inconsistent findings about small airway disease existence in CTD-ILD due to uncommon, preferred outcome measurement methods. However, Gomes De Alegria et. al. revealed improvement in small airway disease at post-intervention term which was explained by the existence of changes in bronchiolar level (29). Respiratory muscle strength of CTD-ILD patients was lower than the reference value with current findings (31). The association between respiratory muscle weakness and increased dyspnea, decreased functional capacity, and QoL in SSc-associated ILD has been stated in a previous study (38). Disuse atrophy and physical inactivity were seen (39-40) in CTD-ILD. Contrary to CTD-ILD literature, the effect of PR on muscle strength was detected via restoration of lung functions in other ILDs (41-42). However, there are no study investigated the effect of respiratory muscle training in CTD-ILD. Inconsistency in a change in peripheral muscle strength after PR was indicated in variable reports (28,31). One study found no change in peripheral muscle strength, otherwise, another study found an increase in knee extensor and hand grip strength in the supervised PR group. This was explained by the effect on overall muscle strength of PR programs which consist of aerobic, strengthening exercises. An increase in muscle strength was detected especially with resistance and strengthening exercises in rheumatoid arthritis patients with pulmonary involvement (43). Exercise might provide a restoration in the regulation of inflammation, fibrosis (44), and disease activity (43). Further searches should prescribe modified strengthening exercises for CTD-ILD phenotypes by decreasing joint involvement to a minimum. QoL improved after PR in CTD-ILDs with current findings. This is consistent with previous reports (9). The improvement in QoL in the ninth week according to Dowman et. al. suggests that the length of the prescribed exercise training can affect across all spectrums of CTD- ILD (28). Dowman et. al. found a decline of improvement in QoL in the sixth month post-intervention term in CTD- ILD.The sustainability of exercise training reinforces permanent improvements in QoL (45). Also, self-management is part of the PR benefit of tolerating exercise. Current findings strengthened the necessity of the use of PR more commonly in clinical practice to improve the QoL in patients with SSc-associated ILD like all CTD-ILD phenotypes (46). There was limited evidence of anxiety-depression levels in CTD-ILD patients in the current findings. There were enormous studies about anxiety, and depression levels of ILDs, otherwise, insufficient evidence existed in CTD-ILDs. Dowman et. al. showed the relationship between anxiety-depression levels at pre-diagnosis of the disease and patient adherence (28). Previous studies showed that CTD-ILD patients were vulnerable to feeling anxiety and depression easily due to the disease activity (47). It was indicated that systemic manifestations such as the Raynaud phenomenon, and puffy hands that were seen in CTD-ILDs converted into risk factors for change of perception and coping and an increase in anxiety and depression levels even after intervention (48). Fatigue is a widespread manifestation of CTDs (49). Increased fatigue was related to a decrease in DLCO, impaired QoL, increase in dyspnea severity, deterioration in exercise capacity, and decreased whole-body muscle strength (49) in ILD patients, consistent with current findings in SSc-associated ILD (31). Supervised breathing, resistance, and aerobic exercises decreased fatigue in the psychosocial activities in Ssc-related ILD patients (31). In contrast to the literature, there was no study investigating the effect of PR on physical activity levels in CTD-ILD. While the severity of the CTD-ILDs increased, the physical activity level decreased (50). Moreover, it was suggested that studies should explore the impact of PR on the disease activity of CTD-ILD.

Limitations

There were some limitations in the included studies which were conflicts in the blinding process (32-28), randomization (29,30), adequate follow-up data, appropriate statistical analysis preference, and homogeneity of groups at baseline (29). These results might not provide new insights to understand the long-term effects of PR. A larger sample size and long-term prospective studies should have been done in the studies to detect accurate suggestions. The current review showed that the use of PR for CTD-ILDs wasn't widespread. Despite the existence of heterogeneity in the use of PR and insufficient data in the related literature, meta-analysis wasn't conducted. Moreover, the improvement in

pulmonary function may be attributed to the referral to a tertiary center, where the therapy was modified, and PR was introduced. Ideally, all other treatments for CTD-ILD should have been in place for at least 3 months and remained unchanged during PR sessions. However, this might not have happened for all included studies in the current systematic review. To date, there hasn't been how exercise response differs in all CTD-ILD phenotypes. Also, not only the exercise part but also the education, self-management, and behavioral adaptation parts of the PR program should be recommended by professionals to conduct further studies. Diagnostic markers, radiographic imaging methods, and cardiopulmonary exercise test should be used in RCTs for outcome measurement to demonstrate the effect of PR with higher evidence.

Conclusion

We anticipate that the current review can serve as the foundation for future research in being usual care of PR in addition to conventional treatment. QoL, mental health, management of dyspnea, and patient adherence are trivets of dealing with CTD-ILDs. Appropriate understanding of the reason can help patients for functional restoration, and improvement of QoL. Acceptance and adherence to PR of CTD-ILD patients should be encouraged with further investigations. With the provided findings, evidence-based information for PR in CTD-ILD patients that can guide monitoring interventions according to disease phenotypes was extracted.

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