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Title: Pulmonary rehabilitation for mild chronic obstructive pulmonary disease: a systematic review

Cristina I. O. Jácome, MSc[1, 2], Alda S. P. D. Marques, PhD[2, 3]

1 Research Centre in Physical Activity, Health and Leisure, Faculty of Sports, University of Porto, Portugal

2 School of Health Sciences, University of Aveiro (ESSUA), Aveiro, Portugal

3 Unidade de Investigação e Formação sobre Adultos e Idosos (UniFAI), Porto, Portugal

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Conflict-of-interest statement

The authors report no conflict of interests.

Contributors

CJ and AM conducted the literature search, decided the articles inclusion and assessed the studies quality. CJ drafted the manuscript and AM revised it critically for important intellectual content and provided final approval of the version to be published.

Corresponding author: Alda Marques, School of Health Sciences, University of Aveiro (ESSUA), Agras do Crasto - Campus Universitário de Santiago, Edifício 30, 3810-193 Aveiro, Portugal. Telephone: 00351 234 372 462. Email: amarques@ua.pt

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Abstract

Introduction: Pulmonary Rehabilitation (PR) is effective in improving exercise capacity and health-related quality of life in patients with moderate-to-very-severe COPD. Quadriceps strength and health-related quality of life (HRQL) can be impaired in patients with mild COPD, therefore, patients at this grade may already benefit from PR. However, the impact of PR in mild COPD remains unestablished. Thus, this systematic review assessed the impact of PR on exercise capacity, HRQL, healthcare resource use and lung function in patients with mild COPD.

Methods: The Web of knowledge, EBSCO, MEDLINE and SCOPUS databases were searched up to April 2013. Reviewers independently selected studies according to the eligibility criteria.

Results: Three studies with different designs (retrospective, one group pretest-posttest and randomized control trial) were included. Outpatient PR programs were implemented in two studies, which included mainly aerobic, strength and respiratory muscle training. The randomized control trial compared a PR home-based program, consisting of 6 months of walking and ball game activities, with standard medical treatment. Significant improvements on exercise capacity (effect size-ES 0.874 and 1.816) and HRQL (ES from 0.236 to 0.860) were found when comparing pre-post data and when comparing PR with standard medical treatment. In one study, a significant decrease in hospitalization days was found (ES 0.380). No significant effects were observed on the number of emergency department visits (ES 0.320), number of hospitalizations (ES 0.219) or lung function (ES 0.198).

Conclusion: Most of the PR programs had significant positive effects on exercise capacity and HRQL of patients with mild COPD however, their effects on healthcare resource use and lung function were inconclusive. This systematic review suggests that patients with mild COPD may benefit from PR; however insufficient evidence is still available. Studies with robust designs and with longer follow-ups should be conducted.

Key words: pulmonary rehabilitation; mild chronic obstructive pulmonary disease; chronic obstructive pulmonary disease

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Introduction

Chronic Obstructive Pulmonary Disease (COPD), independently of its severity, impacts on patients and families lives as well as on healthcare systems [1, 2]. Therefore, it is imperative to plan health care for patients with COPD at all COPD grades.

Pulmonary rehabilitation is defined as "an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities" [3]. This intervention is a recommended standard of care in the management of patients with COPD and typically combines exercise training, education and psychosocial support [3, 4]. A meta-analysis conducted by Lacasse et al. (2006) suggests that pulmonary rehabilitation is effective in relieving dyspnea and fatigue and in improving patients' health-related quality of life [5]. However, in this meta-analysis only studies including patients with moderate, severe and very severe COPD were analyzed.

Recent evidence showed that physical activity levels, quadriceps strength and health-related quality of life can be already impaired in mild COPD (best recorded forced expiratory volume in 1 second (FEV_1) ≥ 80% of the predicted value[6]) [7, 8] and these impairments worsen over time [8]. Therefore, patients at this grade may also benefit from pulmonary rehabilitation programs. A systematic review (2002) about the influence of physical activity on mild to moderate COPD showed that physical activity significantly improved patients' physical fitness, however, no statistically significant benefits were seen on health-related quality of life or dyspnea [9]. Furthermore, the great proportion of patients analyzed in this review had moderate COPD. Therefore, the impact of pulmonary rehabilitation programs in mild COPD remains unestablished.

Thus, this systematic review aimed to assess the impact of pulmonary rehabilitation on exercise capacity, health-related quality of life, healthcare resource use and lung function in patients with mild COPD.

Methods

Search strategy

A systematic literature search was conducted between January and April 2013 on the following databases: Web of knowledge (1970-2013), EBSCO (1974-2013), MEDLINE (1948-2013) and

SCOPUS (1960-2013). The search terms used were organized using the PICO (Population, Intervention, Comparison and Outcome) framework [10], the definition of Comparison (C) was omitted as it was aimed to find a range of study designs: [(COPD OR "chronic obstructive pulmonary disease" OR "chronic bronchitis" OR emphysema OR "mild COPD" OR "early COPD" OR "GOLD 1" OR "GOLD I") AND ("pulmonary rehabilitation" OR "respiratory rehabilitation" OR "exercise training" OR "physical activity" OR exercise)] AND ("exercise capacity" OR "health-related quality of life" OR "healthcare resource use" OR "lung function" OR "FEV_1"). The reference lists of the included studies were hand searched for other potentially eligible studies. This systematic review was reported according to the PRISMA statement for preferred reporting items for systematic reviews and meta-analyses [11].

Selection criteria

According to the PICO framework, studies were included if they met the following inclusion criteria:

i) Patients with mild COPD (FEV_1 ≥80% of the predicted [6]);

ii) Pulmonary rehabilitation program (inpatient, outpatient or home-based) of at least four weeks [4, 5], that included exercise training with or without any form of education and/or psychological support;

iii) Comparison: Standard medical treatment or none;

iv) Outcomes: at least one of the following - exercise capacity, health-related quality of life, healthcare resource use and lung function.

Studies were excluded if they did not include patients with mild COPD (studies with a subgroup of patients were retained in the analysis) and if they were review papers, abstracts of communications or meetings, conference proceedings papers, case reports, editorials, commentary to articles, study protocols or unpublished papers. Papers without abstracts or written in languages other than English, Portuguese and Spanish were also excluded.

Screening of studies

The authors independently reviewed the titles, abstracts and keywords of every record. If the information given in the title, abstract and or keywords suggested that the study might fit the inclusion criteria of the systematic review, the full article was retrieved for further assessment. From

the full articles, the decision to exclude a study was based on agreement of both authors. Disagreements were solved by reaching a consensus. Studies that did not fulfill the selection criteria of the systematic review were excluded. Once a study was excluded, a record of the article, including the reason for exclusion, was retained.

Quality assessment

The methodological quality of each included study was independently assessed by the two authors, based on the checklist created by Downs and Black (1998) [12]. This checklist assesses the quality of both randomized and non-randomized studies of health care interventions and it is composed of 27 questions split into 5 sections: reporting; external validity; internal validity – bias; internal validity – confounding and power [12]. According to previous systematic reviews [13, 14], the scoring for question 27 dealing with statistical power was simplified to a choice of awarding either 1 point or 0 points, depending on whether there was sufficient power to detect a clinically important effect. The scores of the Downs and Black checklist can be grouped into four quality levels: ≤14 poor, 15-19 fair, 20-25 good and 26-28 excellent [13, 14].

Data extraction

The authors independently extracted data from the included studies. Disagreements were discussed until consensus was reached. Data from the articles were extracted in a structured table-format, according to the topics: first author's last name and year of publication, study design, participants' characteristics, type of intervention(s) or comparator(s) (if there was any), outcome measures used and quantitative findings.

Data analysis

To determine the consistency of the quality assessment performed by the two authors, an inter-observer agreement analysis using the Cohen's kappa was performed. The value of Cohen's kappa ranges from 0 to 1 and can be categorized as slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80) or almost perfect (≥0.81) agreement [15]. This statistical analysis was performed using PASW Statistics (version 18.0, SPSS Inc., Chicago, IL).

Due to the different designs and outcome measures used in the selected studies, a meta-analysis was not possible to conduct. To analyze the effects of pulmonary rehabilitation on mild COPD, the

effect sizes were computed for the outcomes of interest. The effect sizes were interpreted as low (0.20), medium (0.50) and high (0.80) effect magnitudes [16]. All quantitative data analyzes were performed using the software Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, New Jersey) [17].

Results

Study selection

The databases search identified 5728 records. After duplicates removal, 4766 records were screened for relevant content. During the title, abstract and keyword screening, 4745 articles were excluded. The full-text of twenty-one potentially relevant articles was assessed and eleven articles were excluded due to the following reasons: i) did not include patients with mild COPD (n=8); ii) did not assess the effect of pulmonary rehabilitation programs with the outcome measures of interest (n=1); iii) did not provide quantitative data (n=1) and iv) were not written in English, Portuguese or Spanish (n=1). Ten studies were retained. Eight of these studies included patients with mild COPD, however results were not presented by COPD grade. The corresponding authors were contacted to provide data on patients with mild COPD. Only Liu et al.[18] made available the requested data and therefore their study was included. The other seven studies were excluded. Therefore, three original articles were included. The search for relevant articles within the reference list of the selected articles did not retrieve any further study (Figure 1).

(insert figure 1 about here)

Quality assessment

The articles included in this review scored 14 to 20 in the Downs and Black scale, with a mean of 16.7±3.1 (Table 1). The agreement between the two authors was substantial (k=0.686; 95% CI 0.507-0.842; p=0.001). Results indicate that the studies quality varied among poor [19], fair [20] and good [18] quality. The three studies scored particularly poor in the following items: description of adverse events, sample representativeness, patient and assessor blinding, adjust for confounding factors in the analysis and power.

(insert table 1 about here)

Study characteristics

Study characteristics are presented in Table 2. The included studies had different designs, i.e., retrospective [19], one group pretest-posttest [20] and randomized control trial [18]. The three studies recruited a total of 100 patients receiving specialized care. Golmohammadi et al. [19] did not provide data on age and gender ratio of the 31 patients with mild COPD included. In the other two studies, age ranged from 41 to 83 years old and male patients included were approximately the double of female patients (47:22).

The pulmonary rehabilitation programs implemented by Golmohammadi et al. [19] and by Riario-Sforza et al. [20] were both outpatient, with duration between 6 and 8 weeks and frequency between 2 and 3 sessions a week. The exercise training sessions lasted between 60 and 90 minutes and included mainly aerobic training, strength training and respiratory muscle training. Both programs included an education component. Liu et al. [18] implemented a home-based pulmonary rehabilitation program, consisting of 1 week of pursed-lip breathing and aerobic training under the supervision of health professionals followed by 6 months of peer-led walking and ball game activities during 60 minutes, twice a week. This study also had a control group that received standard medical treatment, consisting in health education and recommendations to exercise by themselves.

(insert table 2 about here)

Synthesis of the results

Exercise capacity

Exercise capacity was assessed in two studies with the six minute walking distance [18, 20]. Significant improvements on exercise capacity were found when comparing pre-post data (effect size 0.874 [20]) and when comparing PR with standard medical treatment (effect size 1.816 [18]).

Health-related quality of life

Health-related quality of life was measured in two studies using distinct instruments, i.e., the Saint George Respiratory Questionnaire (SGRQ) [19] and the Zhongshan COPD questionnaire [18]. A small improvement in SGRQ symptoms (effect size 0.337) and activity (effect size 0.494) scores and a medium improvement in SGRQ impact score (effect size 0.655) were found after pulmonary rehabilitation [19]. A significant improvement in health-related quality of life (Zhongshan COPD questionnaire total score) favored the pulmonary rehabilitation group (effect size 0.860) [18]. The

Zhongshan COPD questionnaire also provided information on four subscales of health-related quality of life: activity of daily living, social participation, depression and anxiety. Improvements in anxiety (effect size 0.849), activity of daily living (effect size 0.472) and in depression (effect size 0.463) favored the pulmonary rehabilitation group. Social participation did not change significantly in any of the groups (effect size 0.236).

Healthcare resource use

The hospitalization days were decreased after pulmonary rehabilitation (effect size 0.380) [19]. The number of emergency department visits also decreased (effect size 0.320) [19]. The number of hospitalizations in the pulmonary rehabilitation group after 6 months was not statistically significant different from the control group (effect size 0.219) [18].

Lung function

Pulmonary rehabilitation had no significant effect in lung function (effect size 0.198) [18].

Discussion

Most of the pulmonary rehabilitation programs implemented in the three studies analyzed had significant positive effects on exercise capacity and health-related quality of life of patients with mild COPD. However, the effects of these programs on healthcare resource use and lung function were inconclusive.

Two studies analyzed the impact of pulmonary rehabilitation on exercise capacity with the six minute walking test and a statistically significant improvement was found [18, 20]. The improvement in the distance walked after pulmonary rehabilitation was about 37 meters in one study [18] and 63 meters in the other [20]. Since the minimal important difference for the six-minute walking test is expected to be between 25 and 35 meters in patients with moderate and severe COPD [21, 22], we can hypothesize that in both studies the clinically important effect was achieved. Nevertheless, this has to be interpreted with caution, as the minimal important difference for the six-minute walking distance in patients with mild COPD has not been established.

The health-related quality of life was assessed using two instruments, the SGRQ [19] and the Zhongshan COPD questionnaire [23]. In the study of Golmohammadi et al. [19], the improvements were all statistically significant, with the exception of the SGRQ symptoms domain. Lacasse et al. (2006)

and Puhan et al. (2011), reviewing the benefits of pulmonary rehabilitation in COPD, also verified that results of the SGRQ symptoms domain were not statistically significant [5, 24]. These findings suggest that this SGRQ domain may be the less responsive to pulmonary rehabilitation programs. In the study of Liu et al. [18] statistically significant improvements in health-related quality of life favored pulmonary rehabilitation in comparison with the standard medical treatment. The pulmonary rehabilitation programs implemented in the studies by Liu et al. [18] and Golmohammadi et al. [19] improved the health-related quality of life of patients with mild COPD. As physical activity levels and health-related quality of life can be impaired in patients with mild COPD [7, 8] and the limited evidence available shows that these health domains can be improved with pulmonary rehabilitation programs, more studies with robust study designs are needed to establish these benefits at an early stage of the disease.

Prevention of respiratory exacerbations is one of the major goals of COPD management [24]. The effects of pulmonary rehabilitation on the number of exacerbations was not directly assessed in none of the included studies, instead the healthcare resource use was examined. Pulmonary rehabilitation did not have a statistically significant effect on the number of hospitalizations when compared with standard medical treatment [18]. A statistically significant decrease in the number of emergency department visits after pulmonary rehabilitation was also not found, however, a significant decrease in the hospitalization days was observed [19]. In patients with mild COPD, the role of pulmonary rehabilitation in preventing exacerbations and its severity remains unclear. This is mainly due to the lack of studies, but probably also due to the implementation of pulmonary rehabilitation programs with distinct training regimens and therefore, different dose-effects [25].

Pulmonary rehabilitation had no effect on lung function [18]. This was expected, as previous literature showed that no changes in lung function were observed in patients with moderate to very severe COPD after conventional pulmonary rehabilitation programs [26, 27]. However, a matched controlled trial with patients with moderate and severe COPD shows that after three years of outpatient pulmonary rehabilitation, the decline in FEV_1 was significantly lower in the pulmonary rehabilitation group compared to the control group (standard treatment) [28]. In patients with mild COPD, it is still unknown if in the long run pulmonary rehabilitation can delay the decline of lung function and

therefore the disease progression. This needs to be investigated in well-designed longitudinal studies.

This review has important limitations that need to be considered. First, only three studies with small sample sizes were included and the oldest was published in 2004. This may be due to the difficulty in recruiting patients with mild COPD, since most of them are asymptomatic and do not look for medical assistance. Additionally, this may be a result of the relatively new interest of pulmonary rehabilitation research in mild COPD and of publication bias (studies with statistically significant results are more likely to be published than those with non-significant results). Second, a number of well-designed studies including patients with mild COPD were excluded as results were not individualized by COPD grade. The inclusion of these studies would probably consolidate the findings of this review. Third, all studies had different methodological designs and implemented different pulmonary rehabilitation programs regarding the setting, duration and components. This might be due to the absence of specific guidelines for pulmonary rehabilitation programs for patients with mild COPD. Further research from randomized control trials is therefore needed to define the most appropriate specificities of pulmonary rehabilitation for this population. Fourth, mainly the short term effects of pulmonary rehabilitation were assessed. Only Golmohammadi et al. [19] analyzed the benefits of pulmonary rehabilitation in terms of emergency department visits and hospitalization days one year after pulmonary rehabilitation. However, the long term benefits of pulmonary rehabilitation in terms of exercise capacity and health-related quality of life for patients with mild COPD remains uncertain. Therefore, long term studies are also required.

Conclusions

Most of the pulmonary rehabilitation programs implemented in the included studies had significant positive effects on exercise capacity and health-related quality of life of patients with mild COPD. Nevertheless, the effects of these programs on healthcare resource use and lung function were inconclusive. This systematic review suggests that patients with mild COPD may benefit from pulmonary rehabilitation as part of the management of their disease, however insufficient evidence is still available. Further research with robust study designs and with longer follow-ups is urgently needed to inform guidelines for pulmonary rehabilitation in mild COPD.

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1 Figure captions

2 Figure 1 - PRISMA flow diagram of the included studies.

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Table 1 - Quality assessment in the Downs and Black Scale.

Author (year)	**Reporting**										**External validity**			**Internal validity - bias**							**Internal validity - confounding**						**Power**	**Total**
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Golmohammadi et al. (2004)	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	0	1	1	1	0	0	0	0	0	1	0	14
Riario-Sforza et al. (2009)	1	1	1	1	1	1	1	0	0	1	0	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	16
Liu et al. (2012)	1	1	1	1	1	1	1	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	1	0	20

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Table 2 – Impact of pulmonary rehabilitation programs in patients with mild COPD.

Author (Year)	Design	Participants	Intervention	Outcome Measures	Findings
Golmohammadi et al. (2004)	Retrospective	31 patients with mild COPD	Setting: Outpatient Duration: 6 weeks or 8 weeks Frequency: 2*week or 3*week Exercise training Duration: 90 minutes Components: Breathing exercises, endurance training, upper extremity strength training, inspiratory muscle training Education: adaptations in activities of daily living, relaxation techniques, nutritional counseling, psychosocial support.	SGRQ Symptoms SGRQ Activity SGRQ Impact Emergency department visits Hospitalization days	SGRQ Symptoms: Pre 48.3; Post 42.3; p=0.07 SGRQ Activity: Pre 55.3; Post 48.7; p=0.01 SGRQ Impact: Pre 30.8; Post 23; p=0.01 Emergency department visits: Pre 41.2±13; Post 13.6±7.9; p=0.085 Hospitalization days: Pre 123.9±75; Post 12.9±12.9; p=0.043
Riario-Sforza et al. (2009)	One group pretest-posttest	37 patients with mild COPD 24M:13F 64.6±9.8(41-83)yrs	Setting: Outpatient Duration: 6 weeks Frequency: 2*week Exercise training Duration: 90 minutes Components: warm-up, endurance training, strength training of the arm, shoulder and trunk muscle groups; respiratory muscle training. Education	6MWD	6MWD: Pre 355±63m; Post 418±78m
Liu et al. (2012)	RCT	EG 15 patients with mild COPD 10M:5F 56.4±8.2(46-72)yrs	EG Setting: Home-based Duration: 6 months Frequency: 2*week	6MWD Zhongshan COPD questionnaire: - ADL	EG 6MWD: Pre 407.4±16.9; Post 444.6±22.5; p=0.001 Zhongshan COPD questionnaire ADL: Pre 22±3.1; Post 19.5±2.7; p=0.001

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		Exercise training	- Anxiety	Anxiety: Pre 13.9±2.4; Post 12.3±1.7; p=0.002
	CG	Duration: 60 minutes	- Depression	Depression: Pre 12.3±1.7; Post 11.1±1.4; p=0.011
	17 patients with	Components: walking and ball game activities.	- Social participation	Social participation: Pre12.7±2.5; Post 12.7±1.9; p=0.892
	mild COPD	Education: pursed-lip breathing, aerobic exercises.	- Total score	Total Score: Pre 60.8±5.4; Post 55.7±4.8; p=0.001
	13M:4F		Hospitalizations due to	Hospitalizations: Pre 1.2±0.4; Post 1±0.4; p=0.082
	58.9±6(46-67)yrs	CG	AECOPD	FEV_1: Pre 87.2±4.1%predicted; Post 87.5±3.7%predicted; p=0.442
		Standard medical treatment: health education,	FEV_1	
		advised to continue exercising.		CG
				6MWD: Pre 403.1±21; Post 401.6±26.7; p=0.756
				Zhongshan COPD questionnaire
				ADL: Pre 21.3±3.2; Post 20.8±2.8; p=0.324
				Anxiety: Pre 14±2.9; Post 14.35±2.9; p=0.496
				Depression: Pre 12.1±2.0; Post 11.9±2; p=0.699
				Social participation: Pre 12.7±2.5; Post 12.2±2.3; p=0.245
				Total score: Pre 60.1±4; Post 59.2±3.3; p=0.440
				Hospitalizations: Pre 1.3±0.6; Post 1.1±0.5; p=0.083
				FEV_1: Pre 87.7±5%predicted; Post 86.7±4.3%predicted; p=0.221

Data are presented as mean±standard deviation.

COPD: Chronic obstructive pulmonary disease; SGRQ: St. George's Respiratory Questionnaire; M: male; F: female; RCT: randomised control trial; 6MWD: six minute walking distance; EG: experimental group; CG: control group; ADL: activities of daily living; AECOPD: acute exacerbation of COPD; FEV_1: forced expiratory volume in 1 second.

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