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Impact of pulmonary rehabilitation in patients with mild chronic obstructive pulmonary disease

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Title: Impact of pulmonary rehabilitation in patients with mild chronic obstructive pulmonary disease

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Conflicts of Interest

The authors report no conflict of interest.

Contributors

CJ implemented the intervention and drafted the manuscript and AM revised it critically for important intellectual content and provided final approval of the version to be published.

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Abstract

Introduction: Pulmonary Rehabilitation (PR) is a core component of the management of patients with moderate-to-very-severe Chronic Obstructive Pulmonary Disease (COPD). However, as impairments in quadriceps muscle strength and health-related quality of life (HRQL) are already present in patients with mild COPD, there is a need to investigate if PR could also be beneficial to these patients. Thus, this study assessed the impact of PR in patients with mild COPD.

Methods: A quasi-experimental study was conducted. Twenty-six participants (67.8±10.3yrs; forced expiratory volume in 1 second 86.2±7.9% predicted) enrolled in a 12-week PR program with exercise training and psychoeducation. Lung function was assessed with spirometry, dyspnea with the Modified British Medical Research Council questionnaire, functional balance with the Timed Up and Go test; muscle strength with the 10 repetition maximum testing; exercise tolerance with the 6-minute walking test; emotional state with the Depression, Anxiety and Stress Scales and HRQL with the St. George's Respiratory Questionnaire (SGRQ).

Results: Significant effects were observed on participants' dyspnea ($p=0.003$; effect size-ES=0.7), functional balance ($p<0.001$; ES=0.8), shoulder flexors/knee extensors strength ($p<0.001$; ES=1.2-1.3) and exercise tolerance ($p<0.001$; ES=0.5). With the exception of the SGRQ impact score, the symptoms ($p<0.001$; ES=0.6), activities ($p=0.02$; ES=0.4) and total ($p=0.005$; ES=0.3) scores improved significantly after PR. The PR program had no significant effect on participants' lung function and emotional state.

Conclusions: Patients with mild COPD benefit from PR and could therefore be routinely included in these programs. Studies with more robust designs and with long-term follow-ups are needed to inform guidelines for PR in mild COPD.

Key Words: Chronic obstructive pulmonary disease; pulmonary rehabilitation; early medical intervention.

Introduction

Pulmonary rehabilitation (PR) is *"a comprehensive intervention (…) 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"* [1]. A meta-analysis demonstrated that PR is effective in improving dyspnea and health-related quality of life (HRQL) in patients with moderate-to-very-severe Chronic Obstructive Pulmonary Disease (COPD)[2] and thus, it is currently recognized as a core component of the management of these patients[3].

Recent evidence showed that quadriceps muscle strength and HRQL are already impaired in patients with mild COPD (post-bronchodilator forced expiratory volume in 1 second-FEV_1/forced vital capacity ratio of <0.7 and an FEV_1>80% of the predicted[4])[5]. Therefore, as stated in the American Thoracic Society/ European Respiratory Society statement on PR, there is a need to investigate the potential of PR in these patients[1].

A preliminary study from Riario-Sforza et al. found that, after a 6-week outpatient PR program, patients with mild COPD improved their exercise tolerance[6]. However, the effects of PR on other health domains are still unestablished. Thus, this study aimed to assess the impact of PR on lung function, dyspnea, functional balance, muscle strength, exercise tolerance, emotional state and HRQL of patients with mild COPD. In line with research conducted in more severe grades of COPD, it is hypothesized that patients with mild COPD will also benefit from PR and that these benefits will be observed in different health domains.

Methods

Design and Participants

A quasi-experimental one group pretest-posttest design was used. Outpatients with mild COPD were recruited from two primary care centers. Inclusion criteria were diagnosis of mild COPD according to the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria (post-bronchodilator FEV_1/forced vital capacity ratio of <0.7 and an FEV_1>80% of the predicted)[4], age ≥18 years old and clinical stability for 1 month prior to the study (i.e., no hospital admissions or exacerbations as defined by the GOLD[4]). Patients were excluded if they presented severe psychiatric, neurologic or musculoskeletal conditions[7] and/or unstable cardiovascular disease that could interfere with their performance during the exercise training sessions. The study received full approval from the Institutional Ethics Committee and written informed consent was obtained before data collection.

Intervention

A 12-week PR program with exercise training (3 sessions per week, 60 minutes each) and psychoeducation (1 session per week, 90 minutes) was conducted. The exercise training sessions comprised by:

i. A warm up and a cool down period including range-of-motion, stretching, low-intensity aerobic exercises and breathing techniques (5-10 min)[8].

ii. Endurance training (walking) at 60-80% of the average speed achieved during the 6-minute walking test (6MWT) (20 min)[9]. The training intensity was adjusted according to patient's symptoms on the Modified Borg scale (a rating of 4 to 6 on perceived dyspnea/fatigue was an indicator of adequate training intensity)[1].

iii. Strength training including 7 exercises (2 sets of 10 repetitions) of the major upper and lower limbs muscle groups using free weights and ankle weights (15 min)[10]. The amount of weight was between 50-85% of the 10 repetition maximum (10-RM)[1]. The training progression was based on the two-for-two rule (load was increased when two additional repetitions could be performed on two consecutive sessions)[10] and on patient's symptoms (Modified Borg Scale 4-6)[1].

iv. Balance training consisting of static and dynamic exercises using upright positions (5 min).

In the psychoeducation component the main themes addressed were: information about COPD; medication management; healthy lifestyles; falls and their prevention; emotion-management strategies and community resources.

Data Collection

Socio-demographic and clinical (smoking habits, body mass index, exacerbations in the past 3 months) data were obtained to characterize the sample. Lung function, dyspnea, functional balance, muscle strength, exercise tolerance, emotional state and HRQL were collected before and after the PR program. All questionnaires/tests were administered in a standardized order.

Outcome Measures

Lung function. A spirometric test, using a portable spirometer (MicroLab 3500, CareFusion, Kent, UK), was performed according to standardized guidelines[11].

Dyspnea. Patients reported their activities limitation resulting from dyspnea by selecting the statement from the Modified British Medical Research Council questionnaire that best described their

limitation[4]. The questionnaire comprises five grades (statements) in a scale from 0 to 4, with higher grades indicating greater perceived respiratory limitation. This scale is simple and valid to characterize the impact that dyspnea has on activities of patients with COPD[4] and variations of 1 point indicate a perceived clinical improvement[12].

Functional balance. The Timed Up and Go test was used to assess functional balance[13]. The test requires the patient to rise from a standard chair, walk 3 meters, turn around, walk back to the chair and sit down. Patients were instructed to walk quickly, but as safely as possible. Two tests were performed and the best performance was considered.

Muscle strength. The muscle strength of the shoulder flexors and of the knee extensors of the dominant limbs was assessed using the 10-RM with ankle and free weights. In patients with COPD, the completion of 1-RM testing may not be advisable or safe[14], thus multiple RM, such as 10-RM, have been used[15]. The 10-RM testing was considered the maximum amount of weight that could be moved through the full range of motion 10 times, with the proper technique and without compensatory movements[10].

Exercise tolerance. Exercise tolerance was measured using the 6MWT. The measurement properties of this test are well established in COPD and it has showed similar peak rate of oxygen uptake and heart rate as an incremental cycle ergometer test[16]. Two tests were performed according to the protocol described by the American Thoracic Society[17] and the best performance was considered. The minimal important difference (MID) for the 6MWT is 25 meters in patients with COPD[18].

Emotional state. The Depression, Anxiety, Stress Scales (DASS) measure the negative emotional states of depression, anxiety and stress[19]. Each sub-scale has seven items and the participant is asked to use a 4-point (from 0 to 3) severity scale to rate the extent to which they have experienced each state over the past week. Internal consistency has been shown to be acceptable for all three scales (Cronbach's alphas between .82 and .93)[20]. Consistent with convention, all DASS-21 scores were doubled to facilitate comparison with previous research and norms established using the DASS-42. The maximum score of the DASS-42 is 42 in each of depression, anxiety and stress scales and higher scores indicate high levels of emotional distress.

Health-related quality of life. The St. George's Respiratory Questionnaire (SGRQ) is a disease-specific instrument designed to measure quality of life in patients with chronic lung disease[21]. The

questionnaire has three domains: symptoms, activities and impact. SGRQ presented high internal consistency with Cronbach's alphas >.7 in the sub-domains and >.9 in the overall questionnaire[22]. For each domain and for the total questionnaire, score ranges from 0 (no impairment) to 100 (maximum impairment). A change of 4 units is considered clinically relevant[21].

Statistical Analysis

Using 6MWT data from the study of Riario-Sforza et al. (effect size=0.88)[6], a sample size estimation with 95% power (α=0.05) was performed. This power analysis determined that a statistically significant difference in 6MWT after a PR program would be detected with 19 subjects. As PR programs have considerable dropouts, varying between 20-40%[23, 24], 30 patients were recruited. Descriptive statistics were used to describe the sample. For each outcome measure, the normality of data was investigated with the Shapiro–Wilk test. Paired t-tests for normally distributed data and Wilcoxon signed-rank tests for ordinal/non-normally distributed data were used to compare pre- and post-PR variables. The level of significance was set at 0.05. These analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA).

Statistical analysis was completed with the estimation of effect sizes indices, which evaluate the magnitude of treatment effect[25]. The formula Cohen's dz was used (mean change score divided by the standard deviation of change), as this is the effect size index recommended for matched pairs[26]. Cohen's dz for each outcome measure was calculated using the G*Power 3 software (University Düsseldorf, Germany) and was interpreted as a small (≥0.2), medium (≥0.5) or large (≥0.8) effect[27].

Results

Thirty patients enrolled in the study, however 4 (13.3%) dropped-out due to overlap between the program schedule and professional activities (n=1), relocation (n=1), respiratory exacerbation (n=1) and no reason given (n=1). Therefore, 26 participants (16 males; age 67.8±10.3 years old) completed the study. Table 1 provides the characteristics of the participants.

(insert table 1 about here)

The PR program had no effect on lung function (pre 83.8% predicted vs. post 84.1% predicted; p=0.73) (table 2). A reduction in participants' dyspnea was observed (pre median [interquarlile range] 1[1,2] vs. post 1[0,1]; p=0.003; ES=0.7), with more than half of participants (n=16; 61.5%) presenting a mMRC variation >1. Significant improvements were also verified on functional balance (pre 7.8s vs. 6.7s; p<0.001), muscle strength (shoulder flexors pre 2.3kg vs. post 3.6kg; knee extensors pre 4.1kg

vs. post 6.7kg; p<0.001) and exercise tolerance (pre 432m vs. post 464m; p<0.001), with medium and large effects sizes (from 0.5 to 1.3) (table 2). However, no differences were found for the emotional states of depression (pre median 6 vs. post 4; p=0.65), anxiety (pre median 6 vs. post 5; p=0.82) and stress (pre median 10 vs. post 8; p=0.63). The SGRQ total score (pre 31.3 vs. post 25; p=0.005; ES=0.3), the SGRQ symptoms score (pre 46.3 vs. post 34.7; p<0.001; ES=0.6) and the SGRQ activities score (pre 44 vs. post 34.8; p=0.02; ES=0.4) improved significantly after PR, reaching the MID (4 units)[21]. However, there was no significant improvement on the SGRQ impact score (pre 19.4 vs. post 16.3; p=0.14).

(insert table 2 about here)

Discussion

According to our knowledge, this was the first study to investigate the effects of PR on different health domains in patients with mild COPD. The main finding was that a 12-week PR program was effective in improving patients' dyspnea, functional balance, muscle strength, exercise tolerance and HRQL. A perceived clinical improvement on dyspnea was observed in >50% of patients, in line with the existing evidence on the benefits of PR in patients with moderate-to-very-severe COPD[12]. This result demonstrates that patients with mild COPD already experience restrictions in their daily life due to dyspnea and that PR has the potential to reverse this situation. Regarding the effect of the program on patients' functional balance, a change of -1.1±1 seconds on TUG score was found. This change is lower than that obtained by Beauchamp et al. (-1.5±2.4 seconds), which examined the effect of a standard PR program on balance of patients with more severe COPD grades (mean FEV_1 46.3±22.3%)[28]. However, this result is not surprising since patients with mild COPD had better baseline scores compared with patients included in the previous mentioned study, and thus less potential to further improve their functional balance was expected. Increases of 56.5% on shoulder flexors and of 63.4% on knee extensors muscle strength were verified. These results are difficult to interpret in the absence of published MID values for the 10-RM. Nevertheless, the percentage changes found are similar to previous research (a 56.3% increase in chest pull exercise and 88.2% in leg extension)[29].

The improvement in the distance walked after PR was about 32 meters. Considering that 25 meters is the MID for the 6MWT in patients with COPD[18], it could be assumed that this study achieved the clinically important effect. However, this MID was established based on a sample of patients with a

wide range of disease severity and may not represent a clinically important effect for patients with mild COPD. Future studies should determine the MID for the 6MWT in patients with mild COPD to contribute for clinical decision-making in this COPD population.

An improvement in the SGRQ total score of about 6 units was also observed, exceeding the 4 units considered clinically relevant[21]. This result demonstrates that HRQL in patients with mild COPD, even if not severely affected (baseline scores of 31.3 in 100), can be improved with PR. Contrary to the symptoms and activities domains, the impact domain was not significantly different after PR. Patients with mild COPD might not experience yet relevant disturbances in social and psychological functioning in their daily life, demonstrated by the low impact scores found at baseline (19.4 in 100)[5], and therefore this domain had less potential to be improved.

The PR program had no effect on lung function, which is in accordance with the short-term effects of PR[30]. However, a longitudinal study with patients with moderate-to-severe COPD showed that, after three years, the decline in FEV_1 was significantly lower in the PR group compared to the standard care group[31]. The potential of PR in delaying the decline of lung function should therefore be examined in patients with mild COPD as well. Patients' emotional state also did not improve after the intervention. However, significant benefits in the emotional function of patients with moderate-to-very-severe COPD after PR programs have been described[2]. Since patients' baseline scores on DASS were only slightly higher than normative values (depression 6 vs. 2; anxiety 6 vs. 2; stress 10 vs. 8)[20], one possible reason for this result may be that patients with mild COPD may not yet experience significant emotional distress.

The overall findings suggest that PR is effective in improving dyspnea, functional balance, muscle strength, exercise tolerance and HRQL in patients with mild COPD. Thus, the critical question for future studies should move from *"should patients with mild COPD be integrated in PR?" to "how should PR be delivered to these patients?"*. Since patients are not referred to hospital-based PR programs until they have advanced COPD[1], less expensive and complex PR programs available at primary care centers could be a promising strategy to deliver PR to patients with mild COPD. These programs, through the exercise training component, would maintain patients at higher levels of function. Exercise programs in fitness centers with adequate supervision by trained professionals would probably accomplish the same physical benefits of these simple PR programs, with fewer costs; however these programs do not address patients' education and behavior change needs. The

psychoeducation component of PR through collaborative self-management strategies, increases patients' knowledge and skills, key aspects to optimally manage their disease. Therefore, the potential of primary-care based PR to modify the COPD trajectory in patients at earlier grades should be investigated in future COPD research.

This study has some limitations that need to be acknowledged. The absence of a control group is a limitation of this exploratory study. However, as no research has been conducted on this topic, this limitation does not appear to remove the validity and importance of the results found. In future studies, a control group with patients with similar socio-demographic and clinical characteristics should be included. A small sample size was estimated to be sufficient to detect statistically significant differences in the 6MWT, however a larger sample would probably contribute to detect statistically significant differences in the other outcome measures collected, such as DASS and SGRQ impact score. Nonetheless, data from these outcome measures may inform the estimation of sample sizes in future studies. Moreover, the evaluators in this study were the same health professionals that delivered the PR program, which may have influenced the way that outcome measures were assessed. Due to the cross-sectional design, the long-term effects of PR on mild COPD could not be established. Blind randomized control trials with long-term follow-ups are therefore needed.

Conclusion

The PR program was effective in improving dyspnea, functional balance, muscle strength, exercise tolerance and HRQL of patients with mild COPD, suggesting that these patients would benefit of being routinely included in PR programs. Studies with more robust designs and with long-term follow-ups are needed to inform guidelines for PR in mild COPD.

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Outcome Measures

Lung function. A spirometric test, using a portable spirometer (MicroLab 3500, CareFusion, Kent, UK), was performed according to standardized guidelines[11].

Dyspnea. Patients reported their activities limitation resulting from dyspnea by selecting the statement from the Modified British Medical Research Council questionnaire that best described their

limitation[4]. The questionnaire comprises five grades (statements) in a scale from 0 to 4, with higher grades indicating greater perceived respiratory limitation. This scale is simple and valid to characterize the impact that dyspnea has on activities of patients with COPD[4] and variations of 1 point indicate a perceived clinical improvement[12].

Functional balance. The Timed Up and Go test was used to assess functional balance[13]. The test requires the patient to rise from a standard chair, walk 3 meters, turn around, walk back to the chair and sit down. Patients were instructed to walk quickly, but as safely as possible. Two tests were performed and the best performance was considered.

Muscle strength. The muscle strength of the shoulder flexors and of the knee extensors of the dominant limbs was assessed using the 10-RM with ankle and free weights. In patients with COPD, the completion of 1-RM testing may not be advisable or safe[14], thus multiple RM, such as 10-RM, have been used[15]. The 10-RM testing was considered the maximum amount of weight that could be moved through the full range of motion 10 times, with the proper technique and without compensatory movements[10].

Exercise tolerance. Exercise tolerance was measured using the 6MWT. The measurement properties of this test are well established in COPD and it has showed similar peak rate of oxygen uptake and heart rate as an incremental cycle ergometer test[16]. Two tests were performed according to the protocol described by the American Thoracic Society[17] and the best performance was considered. The minimal important difference (MID) for the 6MWT is 25 meters in patients with COPD[18].

Emotional state. The Depression, Anxiety, Stress Scales (DASS) measure the negative emotional states of depression, anxiety and stress[19]. Each sub-scale has seven items and the participant is asked to use a 4-point (from 0 to 3) severity scale to rate the extent to which they have experienced each state over the past week. Internal consistency has been shown to be acceptable for all three scales (Cronbach's alphas between .82 and .93)[20]. Consistent with convention, all DASS-21 scores were doubled to facilitate comparison with previous research and norms established using the DASS-42. The maximum score of the DASS-42 is 42 in each of depression, anxiety and stress scales and higher scores indicate high levels of emotional distress.

Health-related quality of life. The St. George's Respiratory Questionnaire (SGRQ) is a disease-specific instrument designed to measure quality of life in patients with chronic lung disease[21]. The

questionnaire has three domains: symptoms, activities and impact. SGRQ presented high internal consistency with Cronbach's alphas >.7 in the sub-domains and >.9 in the overall questionnaire[22]. For each domain and for the total questionnaire, score ranges from 0 (no impairment) to 100 (maximum impairment). A change of 4 units is considered clinically relevant[21].

Statistical Analysis

Using 6MWT data from the study of Riario-Sforza et al. (effect size=0.88)[6], a sample size estimation with 95% power (α=0.05) was performed. This power analysis determined that a statistically significant difference in 6MWT after a PR program would be detected with 19 subjects. As PR programs have considerable dropouts, varying between 20-40%[23, 24], 30 patients were recruited. Descriptive statistics were used to describe the sample. For each outcome measure, the normality of data was investigated with the Shapiro–Wilk test. Paired t-tests for normally distributed data and Wilcoxon signed-rank tests for ordinal/non-normally distributed data were used to compare pre- and post-PR variables. The level of significance was set at 0.05. These analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA).

Statistical analysis was completed with the estimation of effect sizes indices, which evaluate the magnitude of treatment effect[25]. The formula Cohen's dz was used (mean change score divided by the standard deviation of change), as this is the effect size index recommended for matched pairs[26]. Cohen's dz for each outcome measure was calculated using the G*Power 3 software (University Düsseldorf, Germany) and was interpreted as a small (≥0.2), medium (≥0.5) or large (≥0.8) effect[27].

Results

Thirty patients enrolled in the study, however 4 (13.3%) dropped-out due to overlap between the program schedule and professional activities (n=1), relocation (n=1), respiratory exacerbation (n=1) and no reason given (n=1). Therefore, 26 participants (16 males; age 67.8±10.3 years old) completed the study. Table 1 provides the characteristics of the participants.

(insert table 1 about here)

The PR program had no effect on lung function (pre 83.8% predicted vs. post 84.1% predicted; p=0.73) (table 2). A reduction in participants' dyspnea was observed (pre median [interquarlile range] 1[1,2] vs. post 1[0,1]; p=0.003; ES=0.7), with more than half of participants (n=16; 61.5%) presenting a mMRC variation >1. Significant improvements were also verified on functional balance (pre 7.8s vs. 6.7s; p<0.001), muscle strength (shoulder flexors pre 2.3kg vs. post 3.6kg; knee extensors pre 4.1kg

vs. post 6.7kg; p<0.001) and exercise tolerance (pre 432m vs. post 464m; p<0.001), with medium and large effects sizes (from 0.5 to 1.3) (table 2). However, no differences were found for the emotional states of depression (pre median 6 vs. post 4; p=0.65), anxiety (pre median 6 vs. post 5; p=0.82) and stress (pre median 10 vs. post 8; p=0.63). The SGRQ total score (pre 31.3 vs. post 25; p=0.005; ES=0.3), the SGRQ symptoms score (pre 46.3 vs. post 34.7; p<0.001; ES=0.6) and the SGRQ activities score (pre 44 vs. post 34.8; p=0.02; ES=0.4) improved significantly after PR, reaching the MID (4 units)[21]. However, there was no significant improvement on the SGRQ impact score (pre 19.4 vs. post 16.3; p=0.14).

(insert table 2 about here)

Discussion

According to our knowledge, this was the first study to investigate the effects of PR on different health domains in patients with mild COPD. The main finding was that a 12-week PR program was effective in improving patients' dyspnea, functional balance, muscle strength, exercise tolerance and HRQL. A perceived clinical improvement on dyspnea was observed in >50% of patients, in line with the existing evidence on the benefits of PR in patients with moderate-to-very-severe COPD[12]. This result demonstrates that patients with mild COPD already experience restrictions in their daily life due to dyspnea and that PR has the potential to reverse this situation. Regarding the effect of the program on patients' functional balance, a change of -1.1±1 seconds on TUG score was found. This change is lower than that obtained by Beauchamp et al. (-1.5±2.4 seconds), which examined the effect of a standard PR program on balance of patients with more severe COPD grades (mean FEV_1 46.3±22.3%)[28]. However, this result is not surprising since patients with mild COPD had better baseline scores compared with patients included in the previous mentioned study, and thus less potential to further improve their functional balance was expected. Increases of 56.5% on shoulder flexors and of 63.4% on knee extensors muscle strength were verified. These results are difficult to interpret in the absence of published MID values for the 10-RM. Nevertheless, the percentage changes found are similar to previous research (a 56.3% increase in chest pull exercise and 88.2% in leg extension)[29].

The improvement in the distance walked after PR was about 32 meters. Considering that 25 meters is the MID for the 6MWT in patients with COPD[18], it could be assumed that this study achieved the clinically important effect. However, this MID was established based on a sample of patients with a

wide range of disease severity and may not represent a clinically important effect for patients with mild COPD. Future studies should determine the MID for the 6MWT in patients with mild COPD to contribute for clinical decision-making in this COPD population.

An improvement in the SGRQ total score of about 6 units was also observed, exceeding the 4 units considered clinically relevant[21]. This result demonstrates that HRQL in patients with mild COPD, even if not severely affected (baseline scores of 31.3 in 100), can be improved with PR. Contrary to the symptoms and activities domains, the impact domain was not significantly different after PR. Patients with mild COPD might not experience yet relevant disturbances in social and psychological functioning in their daily life, demonstrated by the low impact scores found at baseline (19.4 in 100)[5], and therefore this domain had less potential to be improved.

The PR program had no effect on lung function, which is in accordance with the short-term effects of PR[30]. However, a longitudinal study with patients with moderate-to-severe COPD showed that, after three years, the decline in FEV_1 was significantly lower in the PR group compared to the standard care group[31]. The potential of PR in delaying the decline of lung function should therefore be examined in patients with mild COPD as well. Patients' emotional state also did not improve after the intervention. However, significant benefits in the emotional function of patients with moderate-to-very-severe COPD after PR programs have been described[2]. Since patients' baseline scores on DASS were only slightly higher than normative values (depression 6 vs. 2; anxiety 6 vs. 2; stress 10 vs. 8)[20], one possible reason for this result may be that patients with mild COPD may not yet experience significant emotional distress.

The overall findings suggest that PR is effective in improving dyspnea, functional balance, muscle strength, exercise tolerance and HRQL in patients with mild COPD. Thus, the critical question for future studies should move from *"should patients with mild COPD be integrated in PR?" to "how should PR be delivered to these patients?"*. Since patients are not referred to hospital-based PR programs until they have advanced COPD[1], less expensive and complex PR programs available at primary care centers could be a promising strategy to deliver PR to patients with mild COPD. These programs, through the exercise training component, would maintain patients at higher levels of function. Exercise programs in fitness centers with adequate supervision by trained professionals would probably accomplish the same physical benefits of these simple PR programs, with fewer costs; however these programs do not address patients' education and behavior change needs. The

psychoeducation component of PR through collaborative self-management strategies, increases patients' knowledge and skills, key aspects to optimally manage their disease. Therefore, the potential of primary-care based PR to modify the COPD trajectory in patients at earlier grades should be investigated in future COPD research.

This study has some limitations that need to be acknowledged. The absence of a control group is a limitation of this exploratory study. However, as no research has been conducted on this topic, this limitation does not appear to remove the validity and importance of the results found. In future studies, a control group with patients with similar socio-demographic and clinical characteristics should be included. A small sample size was estimated to be sufficient to detect statistically significant differences in the 6MWT, however a larger sample would probably contribute to detect statistically significant differences in the other outcome measures collected, such as DASS and SGRQ impact score. Nonetheless, data from these outcome measures may inform the estimation of sample sizes in future studies. Moreover, the evaluators in this study were the same health professionals that delivered the PR program, which may have influenced the way that outcome measures were assessed. Due to the cross-sectional design, the long-term effects of PR on mild COPD could not be established. Blind randomized control trials with long-term follow-ups are therefore needed.

Conclusion

The PR program was effective in improving dyspnea, functional balance, muscle strength, exercise tolerance and HRQL of patients with mild COPD, suggesting that these patients would benefit of being routinely included in PR programs. Studies with more robust designs and with long-term follow-ups are needed to inform guidelines for PR in mild COPD.

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Table 1- Socio-demographic and clinical characteristics of the participants (n=26).

Characteristics	Result
Age (yrs)	67.8±10.3
Male	16(59.3%)
BMI (kg/m^2)	28.7±5.01
Smokers	7(25.9%)
Exacerbations past 3 months	
0	14(53.9%)
1-2	7(26.9%)
≥3	5(19.2%)
FEV_1 (L)	2±0.4
FEV_1 (% predicted)	83.8±5.4

Note: values show mean±SD or n(%) unless otherwise indicated. Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second.

Table 2 - Effect of PR on lung function, dyspnea, functional balance, muscle strength, exercise tolerance, emotional state and health-related quality of life (n=26).

Variable	Pre-PR	Post-PR	p-value	ES
FEV_1% predicted	83.8±6.4	84.1±5.4	0.73†	0
mMRC	1[1, 2]	1[0, 1]	0.003‡	0.7
TUG score (s)	7.8±1.5	6.7±1.2	<0.001†	0.8
10-RM shoulder flexors strength (kg)	2.3±0.9	3.6±1.2	<0.001†	1.2
10-RM knee extensors strength (kg)	4.1±2.1	6.7±1.9	<0.001†	1.3
6MWD (m)	432±76	464±76	<0.001†	0.5
DASS-Depression	6[1.5, 9]	4[0.5, 8]	0.65‡	0.2
DASS-Anxiety	6[1.5, 12]	5[2, 10]	0.82‡	0
DASS-Stress	10[5.5, 16]	8[4, 15]	0.63‡	0
SGRQ total score	31.3±18.5	25±17.8	0.005†	0.3
SGRQ symptoms score	46.3±20.2	34.7±21.4	<0.001†	0.6
SGRQ activities score	44±25.2	34.8±24.3	0.02†	0.4
SGRQ impact score	19.4±17.9	16.3±15.4	0.14†	0.2

Note. Values show as mean±SD or Median[interquarlile range]; † paired t-test; ‡ Wilcoxon signed-rank test. Abbreviations: ES, effect sizes; FEV_1, forced expiratory volume in 1 second; mMRC, Modified British Medical Research Council questionnaire; TUG, Timed up and go; 10-RM, 10 repetition maximum; 6MWD, 6-minute walking distance; DASS, Depression, Anxiety and Stress Scale; SGRQ, St. George's Respiratory Questionnaire.