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Evaluation of multidimensional COPD-related subjective fatigue following a Pulmonary Rehabilitation programme

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ABSTRACT (258 words)

Introduction: Subjective fatigue has been recognised as an important, multi-component symptom in COPD. Pulmonary Rehabilitation (PR) improves fatigue component of the Chronic Respiratory Questionnaire, a quality of life (QoL) measure. However, it is not clear if all fatigue dimensions are affected equally. This study aims to evaluate changes in subjective multidimensional fatigue among people with COPD who participated in PR.

Methods: Thirty seven stable COPD patients were recruited; 23 patients (15 male) mean age 68.5 (range 49-86) yrs, mean (SD) % predicted FEV_1 45.3 (19.8); completed 7-weeks of PR. Assessments (pre and post PR) consisted of the Multidimensional Fatigue Inventory (MFI-20), QoL (SGRQ), Anxiety and Depression (HADS), the London Chest Activity of Daily Living Scale (LCADL), muscle strength, incremental (ISWT) and endurance (ESWT) shuttle walk tests. The differences between pre and post PR fatigue were tested using Wilcoxon's test and relationships with other outcomes were examined using Spearman's correlation.

Results: There were statistically significant improvements in Reduced Activity (RA) ($p=0.01$), General (GF) ($p<0.01$) and Physical Fatigue (PF) ($p=0.03$) components of MFI-20 after PR, but there were no differences in Motivation or Mental Fatigue ($p>0.05$). There were significant improvements in ISWT ($p<0.05$), ESWT ($p<0.01$) and muscle strength ($p=0.03$). Statistically significant correlations ($p<0.05$) were found between changes in GF and in both ISWT ($r=-0.43$) and SGRQ impact ($r=0.46$); and between RA and ESWT changes ($r=-0.45$).

Conclusions: Some dimensions of fatigue in COPD are modifiable by a 7- week PR programme. Change in fatigue dimensions in COPD may be associated with a change in maximal or endurance walking distances or QoL.

Keywords: COPD; fatigue; Pulmonary Rehabilitation; disease management

INTRODUCTION

Subjective fatigue is an important and highly prevalent symptom in Chronic Obstructive Pulmonary Disease (COPD) [1]. People with COPD experience greater fatigue than healthy older people [2-4] and this, in turn, is associated with the severity of the disease rather than age itself. COPD-related fatigue (COPD-RF) affects patients' functional performance [5;6], quality of life (QoL) [2;7] and may be an important barrier to undertaking physical activity [8;9]. Fatigue, in COPD is a complex symptom, and as such a multidimensional approach is required to its assessment. The findings from regression studies revealed that dyspnoea, depression, muscle weakness, decreased exercise capacity, airway limitation, body weight and exercise de-saturation were indicators in the perception of COPD-RF [2;3;5;10]. Therefore, these factors should be considered when planning a comprehensive treatment of COPD-RF.

Pulmonary rehabilitation (PR) is a well established gold standard of care for COPD patients, which improves patients' dyspnoea, QoL and exercise tolerance [11;12]. Recent studies have also shown that cognitive function [13], depression and anxiety [14;15] may improve with PR. One meta-analysis demonstrated significant improvement in the fatigue subscale of a QoL questionnaire after PR [16]. However, there is little attention to this outcome in rehabilitation literature and only a few studies considered fatigue as a symptom-specific assessment [17;18]. Although some studies indicate that PR may somewhat modify fatigue in COPD [16;17], it is not clear if the separate general; physical; and psychological aspects of fatigue may be improved equally following PR. Exercise training is an important component of PR leading to improvements in muscle strength and exercise tolerance [19-21], which in turn may influence physical components of COPD-RF. However, rehabilitation also aims to address psychological aspects of COPD using and education and behavioural approaches [22-25], these in turn may modify the motivational and cognitive aspects of fatigue. This study, therefore, aims to evaluate whether COPD-RF dimensions,

assessed with the MFI-20, change after a seven-week PR programme and if the changes in fatigue dimensions are associated with changes in other established outcome measures.

METHODS

Full ethical consent was obtained from the Royal Marsden Local Research Ethics Committee (London, UK). All patients gave written informed consent prior to entering the study.

Subject recruitment

Thirty seven stable COPD subjects (defined as FEV_1/FVC ratio < 0.7) were recruited from those on the waiting list for PR at St. George's Hospital, London (UK) until reaching a desired sample size (see statistical analysis). An invitation letter was sent with a return opt-out slip and those who agreed were contacted by phone. Diagnosis of COPD had been previously confirmed by a general practitioner or a chest physician and medication was optimised. Patients were excluded if they had unstable angina, significant co-morbidities, such as rheumatoid arthritis, stroke, carcinoma, psychiatric personality disorders, intermittent claudication or other mobility limiting conditions. Patients with other mild, stable and well controlled co-morbities were included e.g. osteoarthritis, hypertension or diet-controlled diabetes.

Assessments

Patients included in the study attended the hospital for an individual baseline assessment. Assessment was carried out over two days if necessary, for instance, when the patient was too tired to continue. After attendance of 14 rehabilitation sessions over at least seven and maximum of 10 weeks, the patients were reassessed at the separate follow up session within one week from the last PR session. Those who were unable to complete 14 sessions were classified as dropped-out.

Measurements taken included height (cm), weight (kg) and body composition, assessed using a non-invasive bioelectrical impedance technique (Body composition analyser, Tanita Ltd BC-418MA, UK). Baseline Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC) were assessed using spirometer Micro Plus MS03 (Micro Medical Ltd, Rochester UK) according to ERS/ATS recommendations [26].

Subjective fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20), a 20-item self-report instrument designed to measure subjective fatigue [27;28]. The questionnaire asks patients to describe how they have been feeling lately. For issues of clarity this was specified as “within the last two weeks”. The tool consists of five dimensions covering General Fatigue (GF), Physical Fatigue (PF), Reduced Activity (RA), Reduced Motivation (RM) and Mental Fatigue (MF). Each dimension has 4 items, each item scored from 1-5 with higher scores representing greater levels of fatigue.

Mood status: All participants completed the Hospital Anxiety and Depression Scale (HADS). The HADS is a questionnaire designed to measure depressive and anxiety moods separately [29]. A score of 11 or higher for either of the components indicates probable presence of a mood disorder.

Baseline breathlessness level was assessed using the Medical Research Council Dyspnoea Grade (MRC) [30]. Breathlessness during Daily Activities was assessed using the London Chest Activity of Daily Living Scale (LCADL) [31;31]. The questionnaire consists of 15 daily activities, with each scored 0 to 5. The total score ranging from 0 to 75 is calculated, with the higher score indicating more breathlessness during daily activities.

Health related QoL was assessed using Saint George's Respiratory Questionnaire (SGRQ) [32].

Maximal exercise tolerance was assessed using the Incremental Shuttle Walking Test (ISWT), an incremental, externally paced exercise capacity test conducted according to standardised procedure [33]. Endurance exercise tolerance was then assessed at 85% of peak oxygen uptake (VO_2), estimated from ISWT, using the Endurance Shuttle Walking Test (ESWT) [34]. Prior to and after each test percutaneous arterial oxygen saturation (SpO_2) and heart rate were measured using a pulse oxymeter (Pulsox-3i- Konika Minolta, Singapore) applied to the finger. Borg CR 10 (Breathlessness) and Borg Rating of Perceived Exertion (RPE) scales were scored at the end of each test [35;36].

Quadriceps maximal torque was measured using a "Cybex Norm™ Testing and Rehabilitation System". Concentric knee extensions and flexions were performed and maximally at an angular velocity of 60°/sec. Maximum torque was recorded during isokinetic work of the 10-reperition as the best attempt of the dominant side.

Pulmonary Rehabilitation programme

Subjects underwent a seven week outpatient PR programme with two supervised sessions per week, based in St. George's Hospital, London, UK. Hence, the completed programme consisted of 14 sessions. As this was a "rolling" programme, patients who missed a session(s) could continue beyond 7 weeks until they attended 14 supervised sessions for maximum of 10 weeks. Each session consisted of 1 hour exercise training and 30 minutes of education. The exercise training was designed as circuit training and consisted of an individually tailored programme of aerobic endurance or interval, and upper and lower limbs resistance training. Endurance or interval training were used to achieve exercise intensity of 60-80% VO_2 peak based on ISWT estimation.

The higher intensity was promoted and gradual progression was encouraged each week. Each training session consisted of aerobic training which included cycling, treadmill walking and step climbing. Patients were also encouraged to exercise at home between hospital sessions according to an exercise diary given by the therapist. Education sessions were delivered by a multidisciplinary team and covered pathophysiology, benefits of exercise, self management, breathing control, sputum clearance, medication and oxygen, inhaler techniques, nutrition and diet, relaxation and smoking cessation. Patients were also taught strategies to cope with breathlessness, breathing control and energy conservation techniques.

Statistical analysis

Sample size calculation had been performed prior the study based on mean GF (SD) sub-score of MFI-20 (13.9 (4.2)) from a previous study by Breslin et al. [7]. Assuming change of 3.5 points in MFI-20, the study required minimum 22 patients at power 80% and $p<0.05$. Data from patients who completed 14 PR sessions or dropped out were collected and analysed. Mean and standard deviation (SD) for parametric, and median and inter-quartile range (IQR) for non-parametric variables were recorded. Differences in baseline measurements between the rehabilitation drop-out and completed groups were examined using independent samples parametric or non-parametric tests, as appropriate. Wilcoxon signed-rank tests were performed on the completed PR group to test for differences in pre and post PR results. Spearman's rank correlation was used to identify associations between the changes in fatigue dimensions after PR and other changes in PR outcomes. In all tests a p-value < 0.05 was taken to indicate a statistically significant result. All statistical analysis was carried out in SPSS 15.0.

RESULTS

Thirty seven COPD subjects entered the rehabilitation programme; of these, 23 patients (15 male) completed the programme and were reassessed. Those who completed PR had a mean age of 68.5 years (range 49 - 86), their mean (SD) % predicted FEV_1 was 45.3 (19.8) and FEV_1/FVC ratio 0.44 (0.12). Comparison between this group of patients and those who dropped out from the rehabilitation programme at baseline showed no significant differences in initial fatigue level, age or airway obstruction severity. However, those who dropped out had significantly higher scores for both HADS depression ($p = 0.03$) and anxiety ($p=0.03$); and for SGRQ impact ($p=0.01$) and total ($p = 0.02$). See table 1 for details.

Evaluation of changes in fatigue dimension scores after PR

Most of the 23 patients who completed the rehabilitation programme showed improvements in fatigue score but improvements were not equally distributed across the 5 components of fatigue. A reduction in fatigue was observed in 16 patients for GF and PF scores, 14 for RA, 11 for RM and 9 for MF. See Figure 1 for the individuals' fatigue dimension scores before and after PR.

Median scores for all dimensions except PF vary little pre and post PR. Median scores post PR programme were statistically significantly lower for RA, GF and PF, but not for RM or MF. As can be seen in Figure 2 the IQR change little pre and post PR for GF, PF and RA. However, the IQR is reduced post PR for RM and MF, indicating smaller differences in the scores for the middle 50%. The comparison of median fatigue score before and after rehabilitation showed significant differences only in selected dimensions (see Table 2).

Evaluation of changes in PR outcomes and their association with changes in fatigue scores.

Most patients improved their maximal and endurance walking distance. 17 out of 23 improved on ISWT and 14 out of 20 on their ESWT. At baseline, 11 of the 23 patients showed de-saturation during exercise, defined as a fall of 4% to below 90%, but during reassessment post PR saturation fell in only 8 patients. Although not significant, there was a trend towards improvement in exercise de-saturation.

There were significant differneces in ESWT, ISWT, SGRQ activity scores and mmTq between the start and the end of the PR programme. However, no significant differences were observed in BMI, total SGRQ, LCADL measures or HADS depression or anxiety scores. Summary statistics for PR outcome measures are presented in Table 3.

Relationships between the change in fatigue dimensions following PR and change in the other measurements, as presented in Table 3, were assessed. There were moderate correlations between the change in GF and the change in ISWT (r=-0.43) and for RA and the change in ESWT (r=-0.45). No other significant.relationships were found.

Discussion

This study shows that subjective fatigue is modified following a modest seven week rehabilitation programme and the improvement is evident in three out of five dimensions of MFI-20. Previous studies demonstrated improvement in fatigue component health related QoL after PR as shown by a meta-analysis [16]. Although in a recent RCT [18] of 26 patients no improvement was demonstrated with regard to fatigue frequency, duration, severity or functional limitations following PR, the study was underpowered and the results may be subject to error. The selection of the tool the Fatigue Impact Scale and its responsiveness may also explain the lack of detected

improvement. However, other data presented by Peters et al. [17] a year earlier, implied that unidimentional fatigue, assessed using the Checklist Individual Strength, may be significantly reduced after PR.

Our findings show that there are significant improvements in the Reduced Activity, General and Physical Fatigue components of MFI-20 but not in Reduced Motivation or Mental Fatigue. This study is the first to report changes in individual dimensions of fatigue following PR among patients with COPD. Although PR is a holistic programme, which is intended to address all areas of patients' health, the improvement was demonstrated only in selected fatigue dimensions. There may be various explanations for this finding; our sample size calculation was based on the General Fatigue subscale, which might have not been adequately powered to detect changes in all dimensions. Moreover, the relatively short 7-week programme may be long enough to form changes in general and physical dimensions, but may be insufficient to modify the motivational or mental fatigue. Furthermore, during rehabilitation programme no ambulatory oxygen was used in order to normalise exercise hypoxaemia unless patient was using Long Term Oxygen Therapy or had SpO_2 below 85% on exercise. In this cohort, none of the patients met these criteria therefore no oxygen was offered. An earlier study of fatigue predictors revealed an association between exercise de-saturation and motivational, general and mental fatigue [3]. It is possible that, improvement in exercise oxygenation could have led to greater chages in motivational and mental fatigue. However, as ambulatory oxygen was not used to correct exercise de-saturation in this study this theory remains untested. Suprisingly, there was a trend torward an improvement in exercise oxygenation at the end of PR, which may be due to physiological adaptation following physical training or simply a pulsoxymetric variability [37]. Previous reports in this area are inconsistent [38;39].

Furthermore, an essential component of all PR is physical exercise training and this study showed, as expected, good improvements in exercise tolerance and muscle strength, but not in psychological outcomes such as anxiety or depression. Depression has been shown to be an important predictor of COPD-RF [2;3] and the lack of individual cognitive therapy sessions or depression management in this programme may explain insignificant change in motivational and mental fatigue. However, anxiety and depression in this cohort of patients were mostly within normal values with patients with higher scores more likely to drop out as reflected in recent findings by Hogg et al. [40]. As reported by Harrison and co-workers no improvement in mood should be expected in patients with baseline low scores [41]. Similarly, the scores for motivational and mental fatigue were lower than for the 3 other dimensions, which may indicate mostly normal fatigue values for this cohort. Consequently, the scores for these two dimensions following PR were less likely to improve significantly. Future well powered studies are needed to investigate changes in these psychological dimensions. Furthermore, those patients with higher level of fatigue may show poor uptake and adherence with rehabilitation as shown by Hogg at al. [40] and assessment of fatigue may help in identifying this group of patients.

Analysis of relationships between changes in fatigue and other outcome measures of PR revealed that the increase in maximal exercise tolerance and prolonged endurance walk was associated with the general and activity fatigue dimensions. Previously, studies of fatigue in COPD have shown that general and physical components of fatigue may be predicted by exercise tolerance and muscle strength [3;7;42]. These results lead to the hypothesis that certain dimensions of COPD-RF may be modified by increasing exercise capacity and endurance. In a recent randomised study of PR, effect of fatigue level on outome measures was investigated in patients with higher and lower baseline fatigue. Although both groups improved their walking distance following PR [43], the improvements in distance walked or endurance time achieved at the end

of PR were not maintained after 1 year in the high fatigue group. Also, recent conference data from two authors showed that lack of energy and tiredness are main barriers for physical activity [8;9]. These suggest that higher fatigue may not impact immediate outcomes of PR but it may affect them in a long term. Therefore, subjective fatigue may be one of the important factors considered in the rehabilitation process. Although change in other variables in our study, such as, muscle torque or de-saturation did not relate to changes in fatigue, their role in fatigue improvement cannot be excluded [42;44]. Moreover, there were no changes to BMI following PR, which is in agreement with one other study [45].

Due to limitations in the study design it is not possible to say unequivocally that the changes we observed in fatigue after pulmonary rehabilitation were solely brought about as a result of the rehabilitation. However, previous data from RCTs have indicated a positive effect of rehabilitation on fatigue score [16]. This study was designed, primarily, to test the response of MFI-20 to rehabilitation and to compare the magnitude of change across the dimensions of fatigue. Although this study has been conducted on a relatively small sample of 23 patients, changes in some of the fatigue dimensions have been identified. However, the size of this study does not allow exploration of other factors, such as, drop out reasons or ratio. Fatigue is associated with exacerbation rate [2] which may strongly influence attendance or a drop-out of rehabilitation [40;46]. Although we found no difference in fatigue levels between those who dropped out of the rehabilitation and those who completed, this evaluation was not powered to look at predictors of the drop-out and fatigue may well be an important cofounder or aspect of the drop-out. This may be a scope for future larger studies.

Conclusion

The findings from this study suggest that at least three components of MFI-20 are modifided after 7 week PR. The changes in reduced activity, general and physical fatigue, as might be expected, were associated with improvements in QoL, maximal or

endurance walking distance. However, it is still unclear whether motivational or mental components of fatigue are modified by PR or whether other problem focused modalities are required to achieve improvement in all dimensions of COPD-RF. The multidimensional nature of fatigue requires a holistic approach to treatment which involves physical, nutritional and psychological interventions and it should be taken into consideration when planning individualised patient's care.

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Conflict of interest: Authors have no conflict of interest to be reported in relation to this study.

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