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ORIGINAL ARTICLE

Systemic inflammation in COPD is not influenced by pulmonary rehabilitation

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ABSTRACT

Purpose: Pulmonary rehabilitation is known to lead to improvements in exercise tolerance, health-related quality of life and help reduce symptoms. Exercise, one of the largest components of such an intervention, although of great benefit, can increase the inflammatory response related to chronic obstructive pulmonary disease, depending on intensity and duration. Through this study, the effects of a 12week, high-intensity PR programme on COPD inflammatory-related markers were investigated.

Materials and methods: This study is a longitudinal, observational type of study. Sixty COPD patients were enrolled, 49 of which completed the programme. A 2-h high-intensity PR programme was delivered, twice weekly for 12 weeks. The following markers were assessed at baseline, 4, 8 and 12 weeks through rehabilitation – C-reactive protein, erythrocyte sedimentation rate, neutrophil, eosinophil counts, complete blood count, six-minute walk test and St. George's Respiratory Questionnaire. Serum amyloid A levels were assessed at baseline, week 8 and 12 and exhaled NO at baseline and upon completion of the programme.

Results: This 12-week PR programme resulted in no changes in the inflammatory markers but resulted in significant improvements in both the 6MW distance and health quality of life.

Conclusions: Beneficial effects on functional and HRQoL measures resulted, which, however, appear unrelated to changes in the systemic inflammatory markers.

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Introduction

Chronic obstructive lung disease (COPD) is a respiratory condition characterised by persistent and progressive airflow obstruction with an enhanced chronic inflammatory response in the airways and lungs. Although principally affecting the pulmonary system, comorbidities including chronic heart failure, cardiovascular disease, depression, diabetes, muscle wasting, obesity, weight loss, lung cancer and osteoporosis [1,2] are often found in these patients and contribute to disease severity [3]. Inflammatory effects are mostly noted through marked skeletal muscle alterations [4,5], osteoporosis [6] and cachexia [7], both further contributing to an impairment in the patient's functional status [8,9] and disease progression.

Exercise is highly recommended for these patients, but when carried out at high intensities, this may lead to an inflammatory response in healthy subjects, through an interplay of inflammatory cells, hormones, cytokines, neural and haematological factors [10]. Since COPD patients show signs of systemic inflammation, marked sympathetic activation [11] and muscle wasting [12] during the resting period, it is speculated that following high intensity and prolonged physical activity, there is an increase in these mediators because unaccustomed exercise can lead to muscle and connective tissue damage [13]. However, this response should decrease following repeated exercise since the tissue adapts to the new overload stress [14,15].

Therefore, the intensity of the exercise programme, as well as the duration in which this is carried out play an important role in the systemic reaction to exercise.

The optimal duration of PR programmes has been investigated by these same authors, using the same cohort of patients participating in this study, with results acknowledging these benefits [16]. There is also considerable debate about the appropriate exercise intensity [17]. Troosters et al. [18] reported that in order to reverse the skeletal muscle abnormalities respiratory patients present with, the exercise training should be of high intensity to result in an anabolic stimulus. This helps improve the oxidative capacity of the muscles, leading to enhanced exercise capacity.

Some inflammatory markers commonly analysed in COPD include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), neutrophils and eosinophils and white blood cell counts. CRP and ESR levels are two of the most commonly utilised acute phase proteins and have frequently been noted to be elevated in COPD patients [8,19,20]. These increase further the risk factor for cardiovascular disease, the risk of which is further amplified in the presence of airway obstruction, as there is a direct correlation of these markers with pulmonary inflammation [21]. SAA, another acute-phase protein that is expressed primarily in the liver as part of the systemic response to various injuries and inflammatory stimuli [22], rises with systemic inflammation in a manner similar to that of CRP and ESR [23]. SAA levels were

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elevated both in patients suffering from COPD exacerbations [20,24] as well as in those with stable COPD [25]. Together with these, eosinophilic inflammation is something usually associated as a feature of asthma. As Singh et al. [26] document, eosinophils have been identified in tissue samples from both large and small airways tissue samples taken from patients with stable COPD, which was noted to increase during an exacerbation. Neutrophils, on the other hand, are the most abundant inflammatory cells present in the bronchial wall and lumen of these patients [27].

van Helvoort et al. [28] examined the effects of an acute systemic response following a maximal incremental bicycle test in a group of COPD patients, and reported a marked increase in systemic inflammation as measured by circulating leukocytes and catecholamines, CRP levels were not raised suggesting that the exercise stimulus was insufficient to provoke this response. Muscle damage as measured by creatine kinase was not observed suggesting that the intensity and duration of exercise are stronger determinants of the exercise-induced cytokine response than muscle damage [28]. Rabinovich et al. [29] evaluated the exercise-induced cytokine response after 8 weeks of training in COPD subjects. No differences in plasma levels of cytokines or in TNFα mRNA resulted as taken from the vastus lateralis muscle. This contrasted with results obtained by Greiwe et al. [30] who documented reductions in TNFα in muscle and mRNA from also the vastus lateralis and an increase in protein synthesis in frail elderly subjects after training. Significant differences between the two training programmes exist. The latter provided 3 months of pre-training followed by 3 months of hourly resistive exercises, while Rabinovich et al. [29] used a 6-week programme composed of high frequency and high-intensity cycle ergometry as a tool.

In view of these debates, this study investigated the effects of a 12-week, high-intensity exercise programme on several COPD-related inflammatory markers. The markers were further analysed by classifying the patients according to their Medical Research Council (MRC) dyspnoea score, allowing the researchers to explore the effects also according to the severity of COPD. The aim of this research was to explore the response of these markers to exercise delivered during a PR programme and whether such markers reflect changes obtained in the functional and HRQoL outcome measures following PR.

Materials and methods

This paper reports a longitudinal, observational type of study. All data obtained from this study was recorded at baseline and after 4, 8 and 12 weeks of PR. Outcomes on clinical measures of COPD have already been published [16].

Participants

Seventy-five patients (59 males:16 females), with a confirmed diagnosis of COPD, were referred from the respiratory outpatient clinic of the local general hospital. Patients had a self-reported smoking history, clinical signs and symptoms together with spirometry readings which were consistent with COPD and exertional dyspnoea (MRC grades: 1–4). These participants were all found to be medically stable by the respiratory physicians and pharmacological treatment was assured to be optimal which remained consistent throughout the programme. Eight participants did not meet the inclusion criteria (unstable ischaemic heart disease [$n = 2$], diagnosis of lung cancer [$n = 1$], the presence of mobility problems affecting participation [$n = 3$] and unavailable transport [$n = 2$]). Another seven patients did not accept to participate in the PR programme for various personal reasons. An initial assessment, prior to enrolment was carried out by medical doctors and a physiotherapist. All 60 participants who gave consent to participate were all found to be medically stable and pharmacological treatment was confirmed to be optimal and was not altered during the study.

Ethical considerations

Written information about the programme and the nature of the study was provided to each participant. Signed informed consent was requested and the possibility to voluntarily quit from the study was allowed. All participants' data was coded to ensure patient confidentiality. Prior ethical approval was obtained from the University of Malta Research Ethics Committee (191/2011).

Measurements

Complete blood count, ESR and serum CRP were measured at the hospital laboratory, at baseline, 4, 8 and 12 weeks during rehabilitation. Serum SAA was assessed at baseline, week 8 and week 12 at a research laboratory using a 96-well based human SAA ELISA protocol (Invitrogen, Carlsbad, CA: Cat. No. KHA0011).

Exhaled nitric oxide (NO)

Exhaled NO was measured using a handheld analyser (Niox Mino® Aerocrine Ltd., Solna, Sweden), following a 10-s slow steady exhalation, which was assisted by computer-generated visual and audio biofeedback systems. This instrumentation complies with the ATS and ERS 2005 equipment recommendations for measurement of exhaled NO.

Exercise tolerance rating

The six-minute walking distance test (6MWD) was performed by the researcher according to the ATS guidelines [31] and was repeated twice with an interval of 30 min. The longest distance covered and oxygen saturation were utilised to measure exercise capacity. Dyspnoea was scored using the Borg Category Ratio Scale [32] to measure symptoms before and after the exercise test.

St. George's Respiratory Questionnaire (SGRQ)

The SGRQ consists of 50 items, divided into three domains: symptoms (distress due to respiratory symptoms), activities

(impairment of mobility or physical activity) and effects (psychosocial effects of the disease). The scores range from 0 to l00 for the three subscales with a summary total score. Zero indicated no impairment, while higher scores indicate worse health status. The SGRQ has been shown to have an adequate inter-rater reliability and reproducibility as well as the ability to quantify change over time [33]. This questionnaire was distributed to the participants every 4 weeks to be filled in individually. In the case of any misunderstandings, these were discussed with the researcher.

Intervention

The PR programme consisted of twice weekly 2 h sessions, over a 12-week period. The exercise session consisted of a warm-up period, treadmill walking, with the initial speed devised from the distance obtained from the six-minute walk test and gradually increased throughout the weeks; step-climbing, arm ergometry, cycling using a stationary bike and also upper and lower limb strengthening exercises using weights. Inspiratory muscle training was also carried out using the Respironics IMT Threshold trainer® for 15 min during the class. All participants were instructed to carry the IMT at home for 30 min, 5 d per week. A home exercise programme was also provided to the patients. Educational sessions were also conducted regarding aspects of COPD care and self-management by medical doctors, psychologists, physiotherapists, dieticians and respiratory nurses. These sessions were monitored by a home diary system provided to each participant at the start of the programme. The participants had to reach an intensity of 70% of their maximum heart rate. A high-intensity regime was chosen since it is known to reverse skeletal muscle abnormalities in COPD patients, resulting in an anabolic stimulus improving the oxidative capacity of muscles, enhanced exercise capacity and amelioration of symptoms.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Science (SPSS, Chicago, IL) software (version 23). Patient baseline characteristics and exercise data are presented as mean ± SD (standard deviation). Data were checked for normality using the Shapiro–Wilk test and the data was confirmed to be normally distributed. Statistical inference was conducted either by providing 95% confidence interval for the actual mean outcome measures or by using analysis of variance to compare mean outcome measures between several groups. Pairwise comparisons were carried out using *post hoc* tests, where a .05 level of significance was adopted in all tests.

Results

Forty-nine patients completed the full programme (6 females and 43 males). Three participants stopped after 4 weeks as they were finding no benefit in participation and two had to suspend their rehabilitation after 8 weeks due to personal reasons. The other six were finding rehabilitation physically demanding. Upon commencement, the participants had the following mean parameters: age: 66 years (SD: 7.76), weight: 75 kg (SD: 14.97), BMI: 27.83 (SD 4.81) and height: 164 cm (SD: 7.54). Thirty-one percentage ($n = 15$) of the subjects were classified with an MRC of 2, 29% MRC of 3 ($n = 14$) and 20% with an MRC of 4 and 5 ($n = 10$ each). For statistical reasons, patients were grouped into the mild to a moderate group having an MRC of 2–3 and the severe to the very severe group, having an MRC of 4–5. Baseline patient characteristics are listed in Table 1.

Table 1. Baseline patient demographics represented in mean values and standard deviation.

Patient demographics	Week 0 (Mean values)
Number of patients (Males:Females)	43:6
Age (years)	66 (7.76)
Weight (kg)	75 (14.97)
FEV_1 (l)	1.261 (0.52)
FVC (l)	2.56 (0.81)
PEF (l/Min)	3.02 (1.49)
FEV_1/FVC (l/Min)	49.22 (13.57)
6 MWD (metres)	350.20 (109.40)
SGRQ (impact)	35.65 (17.81)
SGRQ (activity)	58.03 (18.97)
SGRQ (symptom)	45.76 (18.92)
SGRQ (Total)	43.40 (14.88)

Serum CRP, ESR and SAA values

Both the SAA and ESR values increased marginally by 8% and 3%, respectively, whereas the CRP decreased by 26% from 9.57 mg/l to 12.04 mg/l, but escaped significance ($p = .058$) when comparing baseline to the end of rehabilitation after 12 weeks. Interestingly, at the 8th week time point, there was a sharp, non-significant increase in all these three measures. CRP registered a 26% increase from the baseline value and a 40% increase from week 4 to week 8 (Figure 1). This was followed by a significant drop between the 8th and the 12th week of rehabilitation by 41% ($p = .049$). The ESR values increased by from a baseline value of 19.04 mm/h to that of 24.54 mm/h at the 8th week and by 15% between weeks 4 and 8. These values decreased by 20% between the 8th and 12th week but did not reach significance when compared to baseline (Table 2). The more severe patients (MRC 4–5) had higher CRP and ESR levels at the start than the milder group. These then dropped at the end of the 12 weeks of rehabilitation. Increase in ESR values for the more severe group of patients from baseline to the 8th week was lower (17%) than the milder group of patients who had a 42% increase. There was then a decrease in this value from week 8 to the end of the intervention, and this percentage drop was less for the more severe group as compared to the milder group. SAA values at the 8th week time point increased by 42% from 53,456 μg/l to 75,960 μg/l for the total group, 16% for the milder group and 153% for the severe group (Figure 2). Despite this sharp rise, statistical significance was marginally unattained ($p = .058$).

Exhaled nitric oxide levels

Exhaled nitric oxide levels decreased from baseline to the end of rehabilitation, at 12 weeks in both the total group, as

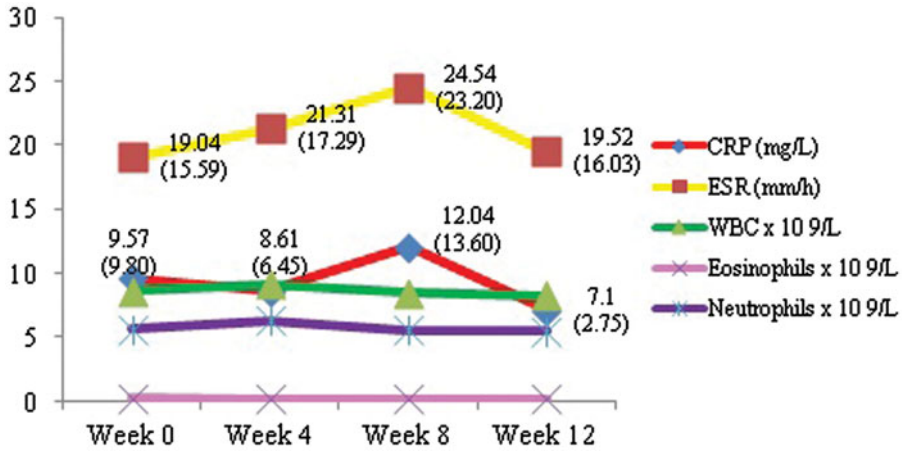

Figure 1. Graph showing changes in markers throughout the 12 weeks of PR. Data for the inflammatory markers given as mean values and their changes throughout the course of rehabilitation together with the standard deviation are noted in the graph.

well as the MRC subgroups (Table 2). The more severe patients had higher levels at the start of the programme (25.64ppb [SD 23.24]) than those with lower MRC levels (18.83ppb [SD 13.40]). The difference in value for the total group amounted to 3.44ppb from a value of 21.03ppb (SD 17.14) at baseline and 17.59ppb (SD 8.68) at week 12.

Other inflammatory markers

Blood eosinophil counts decreased throughout the rehabilitation programme from 0.22×10^9/l (SD: 0.21) at baseline to 0.17×10^9/l (SD: 0.12) at the end of rehabilitation for the total group. This was also noted in patients with an MRC score of 4–5 who started with a value of 0.30×10^9/l (SD: 0.27) and continued to decrease to 0.18×10^9/l (SD: 0.13). Patients with an MRC of 2–3 maintained very similar values throughout the first 8 weeks and then had a slight decline in levels at the 12th week time point from a value of 0.17×10^9/l (SD: 0.13) at baseline to 0.16×10^9/l (SD: 0.11) at the 12th week. The white blood cell count remained within the same range throughout the programme (Figure 1).

Six-minute walk test

Significant improvements in the 6MWD were recorded for the whole patient group after 12 weeks of rehabilitation with a total change of 132.45 m; SD: 127.08 ($p < .001$). The most significant changes were registered in the first 4 weeks (mean total increase of 68.54 m, SD: 91.62; $p < .001$). The changes in exercise tolerance also resulted in significant decreases in the dyspnoea ratings following the exercise tolerance test, from 3.49 (SD: 1.93) to 1.90 (1.56), $p < .001$.

Health-related quality of life

Significant improvements in HR-QoL were noted as early as the first 4 weeks for the total SGRQ score from a score at baseline of 43.40; SD: 14.88 to that of 22.33; SD: 13.37 at the 12th week ($p < .001$). Within the different SGRQ domains, significant changes observed by the 4th week of rehabilitation included activity score with a value of 58.03 at baseline, SD: 18.97 to 38.68; SD: 21.54 ($p = .001$) and the impact (35.65, SD: 17.81 to 13.45, SD: 11.31) and symptom score (45.76, SD: 18.92 to 23.00, SD: 16.65) ($p = .020$ and $p = .002$), respectively.

Discussion

Exercise delivered throughout this 12 week, high-intensity, PR programme did not result in any statistically significant changes in inflammatory markers despite there being significant improvements in exercise tolerance as well as HRQoL measures.

Several studies, as well as the most recent BTS PR guidelines [34–36], have documented that exercise tolerance and HRQoL improve markedly with PR. This was reconfirmed in our study, where functional measures as tested using the 6MWD test improved significantly ($p < .001$) from the 4th week of rehabilitation, which further extended through the following 8 weeks of this programme [16]. Similar changes in all four SGRQ domains were obtained as early as 4 weeks after commencing the programme ($p < .001$). All these changes occurred irrespective of the status of the inflammatory markers which were therefore not contributing factors to these significant improvements. The mechanisms through which rehabilitation is beneficial in these aspects of a patient's care are multi-factorial and as Garrod et al. documented [6] these changes are probably independent of other biological processes which these patients would be experiencing.

Troosters et al. [18] documented that for one to reverse the skeletal muscle abnormalities respiratory patients present with, the exercise training given should be one of high intensity in order to result in an anabolic stimulus. This helps improve the oxidative capacity of the muscles, which in turn leads to enhanced exercise capacity and an accompanying amelioration of symptoms. The use of high-intensity exercise programmes is recommended by other studies including those of Gloeckl et al. [37], Gimenez et al. [38] and Puhan et al. [39].

The baseline measurements for inflammatory markers tended to be high. This may be attributed to the body mass

Table 2. The data obtained throughout the 12-week rehabilitation programme for the outcome measures.

Outcome measures	COPD classification grouping	Week 0 average mean value (SD)	Week 4 average mean value (SD)	Week 8 average mean value (SD)	Week 12 average mean value (SD)	*F* statistics	df1, df2	Partial eta square	*p* value
CRP (mg/l)	Total group	9.57 (9.80)	8.61 (6.45)	12.04 (13.60)	7.10 (2.75)	3.022	1.845, 88.556	0.059	.058
	MRC 2–3	7 (4.16)	7.34 (3.93)	10.28 (12.87)	6.34 (0.97)	1.975	3, 26	0.186	.142
	MRC 4–5	13.30 (13.87)	10.45 (8.73)	14.60 (14.55)	8.20 (3.94)	2.310	3, 17	0.290	.113
ESR (mm/h)	Total group	19.04 (15.59)	21.31 (17.29)	24.54 (23.20)	19.52 (16.03)	1.823	3, 46	.106	.156
	MRC 2–3	15.55 (11.94)	18.03 (9.23)	22.07 (20.40)	15.24 (10.24)	2.430	1.710, 47.89	0.080	.106
	MRC 4–5	24.10 (18.93)	26.05 (24.29)	28.12 (26.91)	25.74 (20.64)	0.354	3, 17	0.059	.787
Eosinophils ($\times 10^9$/l)	Total group	0.22 (0.21)	0.19 (0.14)	0.17 (0.13)	0.17 (0.12)	1.219	3, 46	0.074	.313
	MRC 2–3	0.17 (0.13)	0.17 (0.13)	0.17 (0.15)	0.16 (0.11)	0.110	3, 26	0.013	.953
	MRC 4–5	0.30 (0.27)	0.22 (0.15)	0.16 (0.09)	0.18 (0.13)	2.145	3, 17	0.275	.132
Neutrophils ($\times 10^9$/l)	Total group	5.66 (2.20)	6.34 (2.68)	5.56 (2.16)	5.47 (1.98)	2.213	3, 46	0.126	.099
	MRC 2–3	5.17 (1.66)	5.96 (2.14)	5.44 (2.21)	5.27 (1.79)	1.739	3, 26	0.167	.184
	MRC 4–5	6.37 (2.69)	6.88 (3.30)	5.73 (2.13)	5.77 (2.24)	1.103	3, 17	0.163	.375
SAA (ug/l)	Total group	53,456.44 (49,288.90)		75,960 (62,659.78)	57,638.77 (50,544.67)	1.765	2, 20	0.150	.197
	MRC 2–3	59,319.94 (54,794.18)		68,523.82 (51,836.91)	51,295.58 (40,316.07)	2.638	2, 14	0.274	.107
	MRC 4–5	37,820.44 (28,157.69)		95,789.80 (88,205.62)	74,553.96 (73,360.38)	1.387	2, 4	0.409	.349
WBC ($\times 10^9$/l)	Total group	8.65 (2.58)	9.16 (3.05)	8.47 (2.03)	8.28 (2.25)	1.737	3, 46	0.102	.173
	MRC 2–3	8.03 (1.67)	8.80 (2.47)	8.01 (1.44)	7.75 (1.66)	2.148	3, 26	0.199	.118
	MRC 4–5	9.56 (3.35)	9.69 (3.75)	9.13 (255)	9.06 (2.77)	0.235	3, 17	0.040	.871
6MWD (m)	Total group	350.20 (109.40)	422.86 (101.69)	446.02 (113.29)	482.65 (127.08)	36.174	2.394, 114.90	0.430	**<.001**
Borg Scale at rest	Total group	0.92 (1.37)	0.29 (0.79)	0.08 (0.40)	0.29 (1.34)	20.17	1, 48	0.296	**<.001**
Borg Scale with exercise	Total group	3.63 (1.82)	2.69 (1.81)	2.71 (1.53)	2.08 1.57)	238.64	1, 48	0.833	**<.001**
SGRQ total score	Total group	43.40 (14.88)	34.86 (16.01)	26.81 (16.91)	22.33 (13.37)	260.79	1, 48	0.845	**<.001**
SGRQ activity Score	Total group	58.03 (18.97)	49.86 (21.56)	42.72 (22.75)	38.68 (21.54)	319.92	1, 48	0.870	**<.001**
SGRQ impact score	Total group	35.65 (17.81)	27.01 (16.47)	17.97 (15.88)	13.45 (11.31)	158.58	1, 48	0.768	**<.001**
SGRQ symptom score	Total group	45.76 (18.92)	34.29 (21.55)	30.03 (21.47)	23.00 (16.65)	217.07	1, 48	0.819	**<.001**

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SAA: serum amyloid A; WBC: white blood count; 6MWD: six-minute walking distance; SGRQ: St George's Respiratory Questionnaire. Outcome measures which reached statistical significance are shown in bold. In the SGRQ, the higher the score, the worse is the patient rating.

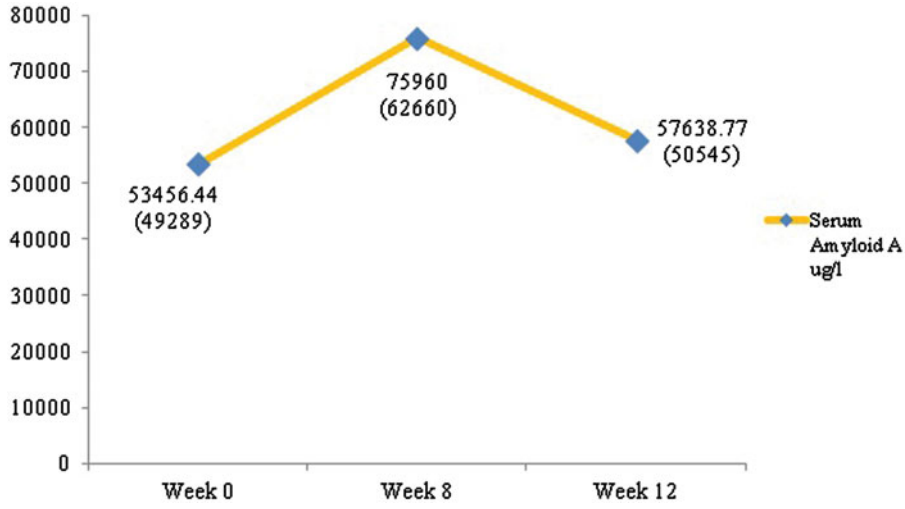

Figure 2. Graph showing changes in SAA mean values (μg/l) and the standard deviation throughout the 12 weeks of PR.

index levels of these patients (BMI: 27.83) since it is known that systemic inflammation is more likely to be present with an increase in body weight [35]. In recent years, as Rodríguez-Hernández report [40], obesity has been associated with chronic systemic inflammation, conditioned by the innate immune system activation in adipose tissue that promotes an increase in proinflammatory cytokines, which in turn trigger the systemic acute-phase response characterised by elevated acute-phase protein levels.

The earlier described initial increase in CRP, ESR and SAA (Table 2) might have been related to muscle fatigue and potential damage which then reached a plateau and decreased again. Exercise initially intensified the whole inflammatory process in view of the muscle disuse these patients had prior to the programme. Canavan et al. [41] report that exercise might actually induce a larger increase in these inflammatory mediators since individual cytokine responses vary greatly depending on the intensity and duration of exercise, the body composition, age and gender of the individual. Strenuous exercise has been associated with increased levels of circulating concentrations of active plasma proteins, with interleukin 6 (IL-6) being a major responder, and leads to the activation of CRP production. The cause for this is muscle injury and repair increased circulating catecholamines and a homeostatic response to maintain glucose supply to exercising muscle. These authors suggest that the increase in IL-6 is related to muscle contractions, to the type of exercise and to the intensity and duration of exercise.

Results from this study may put light on the importance of considering the effects of different exercise intensities depending on the level of baseline fitness of the participants. This causative effect could be the explanation to these changes, on the basis that the measured inflammatory cell counts (white cell count, neutrophils and eosinophil) did not change.

Limitations

The fact that some of the markers (e.g. SAA and exhaled NO) were not assessed at all-time points, might have limited an understanding of the true picture of pathophysiological developments in this study. A more detailed analysis using other inflammatory markers would have provided a better analysis of the whole clinical picture in relation to the prescription and expected benefit of such an exercise programme. The lack of a low-intensity group does not allow for the direct comparison of effects from different intensities. Together with these factors, the small sample size was also a limiting factor. Having a larger sample will give a better perspective of the changes taking place.

Conclusion

The 12-week PR programme described resulted in beneficial effects on functional and HRQoL measures, which however appear unrelated to changes in the systemic inflammatory markers. Further work using different approaches (e.g. low intensity and high repetition-based exercises), is required in order to draw specific conclusions on exercise-induced influences on these markers. Any adaptations that entail remodelling of the muscle are influenced by both the duration and the intensity of daily exercise in order to achieve a steady-state adaptation. Unless this is maintained, all the beneficial effects are lost. Therefore, exercise programme should aim to target as ideal training mode, which can be integrated into the daily lifestyle of these patients, resulting in a long-term beneficial effect both on systemic inflammatory markers and the functional status of these individuals. Further investigations into these factors are therefore highly recommended.

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Disclosure statement

All authors have no conflict of interest to declare.

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