Chapter 7

Does physical training reduce fatigue in sarcoidosis?

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Sarcoidosis Vasc Diffuse Lung Dis 2015; in press

Abstract

Background

Sarcoidosis patients frequently experience fatigue, exercise intolerance and muscle weakness, resulting in reduced quality of life (QoL). Scientific studies on the benefits of physical training in sarcoidosis have been scarce, so the aim of this pilot study was to examine the impact of a 13-week physical training program on fatigue, physical functions and QoL in fatigued sarcoidosis patients and/or patients with exercise intolerance.

Methods

Eighteen sarcoidosis patients participated in a 13-week physical training program. The Fatigue Assessment Scale (FAS), World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF), Medical Research Council (MRC) dyspnea scale, Visual Analogue Scale (VAS), six-minute walk test (6MWT), submaximal bicycle test and muscle strength of the quadriceps and elbow flexors were assessed at baseline and after the program.

Results

FAS scores had decreased (mean difference -2.7 points, 95% CI -4.4 to -1.1) after completion of the training program, along with improvements in WHOQOL-BREF psychological health domain (mean difference 0.9 points, 95% CI 0.2 to 1.7) and MRC dyspnea score (mean difference -0.4 points, 95% CI -0.8 to -0.1). Six-minute walking distance improved by 34.6 m (95% CI 20.3 to 49.0) and mean heart rate on the bicycle test improved (mean difference 8.4 beats/minute, 95% CI -13.8 to -3.0), as did quadriceps strength (mean difference 10.7 kg, 95% CI 5.5 to 15.9).

Conclusion

Fatigue reduced after a period of physical training in sarcoidosis patients. Moreover, psychological health and physical functions improved. Future studies are warranted to assess the benefits of physical training in sarcoidosis.

Introduction

Exercise training has an important role in chronic disease management. It has become the standard in pulmonary rehabilitation (PR) for patients with chronic obstructive pulmonary disease (COPD).[1,2] Exercise training in COPD appears beneficial in improving functional exercise capacity, dyspnea, and quality of life (QoL).[1]

Training programs may benefit not only COPD patients but also other pulmonary disease patients, for example those with interstitial lung diseases (ilds), a heterogeneous group of diagnoses, including sarcoidosis.[1] Studies found that patients with ilds showed improvements similar to those in patients with COPD.[3-6]

Sarcoidosis is an inflammatory disease of unknown etiology, characterized by noncaseating epithelioid cell granulomas, resulting in multiple organ system disorders. Sarcoidosis most commonly affects younger adults. Depending on the organs involved and the severity of the inflammation, patients suffer from a broad range of complaints.[7-10]

Fatigue is the most frequently reported symptom in patients with sarcoidosis.[11-14] Previous studies also showed that exercise intolerance and muscle weakness are frequent symptoms in sarcoidosis, with a persistent character.[13,15-17] It is well-known that fatigue complaints in sarcoidosis affect QoL unfavorably.[18,19] In addition, Marcellis *et al*.[20] recently showed that exercise intolerance is also associated with reduced QoL, suggesting that QoL may be improved by reducing fatigue complaints and exercise intolerance. QoL is an important aspect of the management of chronic patients and refers to the patients' perception or evaluation of their overall functioning in daily life.[21,22]

The etiology of physical impairments in sarcoidosis is multifactorial and the primary causes are still unknown. The disease can involve corticosteroid-induced myopathy, sarcoid muscle and lung involvement, inflammatory processes, and mood disorders.[16,23] In addition, physical inactivity caused by perceived disabling symptoms can induce physical deconditioning, resulting in more perceived fatigue and increased physical inactivity. In the long term, this negative vicious circle of deconditioning may cause exercise intolerance and muscle weakness.[23]

Pharmaceutical treatment options for sarcoidosis to reduce physical impairments, including fatigue, are scarce and also often fail to eradicate these disabling symptoms.[11,24,25] Physical symptoms may be partially reversible by following a structured physical training program. Scientific studies on the benefits of physical training in sarcoidosis have been scarce, as published studies only included patients with ilds other than sarcoidosis[5] or did not perform a subgroup analysis of sarcoidosis patients.[4] Recently, Strookappe *et al*.[6] reported improvements in muscle strength, exercise capacity, and fatigue following a 12-week training program in a small population (n=12) with end-stage refractory sarcoidosis.

The aim of this pilot study was to examine the impact of a 13-week physical training program on fatigue, physical functions, and QoL in fatigued sarcoidosis patients and/or patients with exercise intolerance.

Methods

Subjects

We planned to include 34 sarcoidosis patients with fatigue complaints and/or exercise intolerance, referred for physical therapy by their pulmonologist between January 2013 and December 2013. This pilot study had a single-group pre-post measurement design. The sample size was calculated to detect a change of four points in the FAS score.[26] The power calculation was based on the study by Marcellis *et al*.[13] ((mean baseline FAS score=28±8 points) with a power (1-beta) of 80% and an alpha of 0.05).

Patients were eligible to participate if they (1) reported fatigue complaints (FAS score ≥22 points) and/or a reduced six-minute walking distance (6MWD <predicted 6MWD-50 meters[13]); (2) were in a clinical stable condition with no exacerbation of complaints or changes in initiated therapeutic management during the preceding three months; (3) were between 18 and 70 years old, and (4) were able to participate in a physical training program.

Patients with cognitive impairments and/or unfamiliarity with the Dutch language making them unable to understand questionnaires and instructions were excluded. Other exclusion criteria were (1) severe oncological, cardiac, neurological, or orthopedic disorders making patients unable to participate in a training program and (2) participation in a training program during the six months prior to inclusion.

The diagnosis of sarcoidosis was based on consistent clinical features and bronchoalveolar lavage fluid analysis and/or biopsy-proven noncaseating epithelioid cell granulomas, according to the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines.[9]

This study was approved by the local Medical Ethics Committee of the Maastricht University Medical Centre (MEC 12-3-032.7/ivb). Written informed consent was obtained from all participants.

Demographics

Relevant demographic characteristics and clinical data, including medication use, inflammatory markers, lung function test results, and chest radiographic stages, were obtained at baseline from the medical records.

Clinical data

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured with a pneumotachograph (ZAN 500 bodyplethysmograph, ZAN, Oberthulba, Germany) and the diffusing capacity of the lung for carbon monoxide (DLCO) was measured using the single-breath method with carbon monoxide and methane (ZAN 500 bodyplethysmograph, ZAN, Oberthulba, Germany). Values were expressed as percentage of the predicted value.[27]

C-reactive protein (CRP) concentration was measured by a turbidimetric method on the UniCel Dxc 800 (Beckman Coulter Nederland B.V., Woerden, the Netherlands). The normal value for CRP is <10 mg/l. Serum levels of soluble interleukin-2 receptor (sIL-2R) were analyzed using commercially available Diaclone ELISA kits (Sanquin, Amsterdam, the Netherlands). Normal values are between 240 and 3,154 pg/ml. Serum angiotensin-converting enzyme (ACE) was measured by a colorimetric method (Fujirebio Inc., Tokyo, Japan, cat. no. FU 116). Normal values are between 12 and 68 U/l.

Chest radiographs were graded according to the radiographic staging proposed by DeRemee (0 to III), adding stage IV for patients showing signs of pulmonary fibrosis, loss of lung volume, hilar retraction, and bullae.[9]

Outcome measurements

Physical functions and functioning were measured at baseline and again after 13 weeks at the end of the training program, by a researcher not involved in the training.

Questionnaires

Fatigue was measured with the 10-item Fatigue Assessment Scale (FAS). Each item uses a 5-point rating scale, so FAS scores range from 10 to 50. FAS scores below 22 indicate nonfatigued persons while scores of 22 or higher indicate fatigued persons.[28] The minimal clinically important difference (MCID) of the FAS in sarcoidosis patients is a 4-point or 10% change in FAS score.[11,26]

QoL was measured with the World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF). It consists of 24 questions in four domains (physical health, psychological health, social relationships, and environment) related to QoL and two questions assessing overall QoL and general health aspect. Each question uses a 5-point Likert scale.[29-31]

The Medical Research Council (MRC) dyspnea scale was used to assess the patient's level of perceived dyspnea[32,33] and a Visual Analogue Scale (VAS) to assess the degree of arthralgia and muscle pain.[33]

Exercise capacity and muscle strength

The six-minute walk test (6MWT) was used to assess exercise capacity, and was performed according to the American Thoracic Society guidelines[34], although a 25-m

walking course was used instead of a 30-m course. Before and after the 6MWT, heart rate was measured with a pulse oxymeter, and dyspnea and leg fatigue severity with the Modified Borg Scale.[35] Although the MCID of the 6MWT in sarcoidosis is not known, in patients with COPD this value ranges from 29 m to 54 m and in patients with idiopathic pulmonary fibrosis (IPF) from 24 m to 45 m.[36-40]

Patients performed a submaximal bicycle test on a cycle ergometer. At baseline, the maximal workload (Wmax) was assessed, normal values being 3 Watt/kg for men and 2 Watt/kg for women. Next, submaximal workload was calculated as maximal workload x 80%. This submaximal workload was achieved with a stepwise increase in workload every minute during ten minutes. At the end of the highest achieved workload, heart rate was monitored with a pulse oxymeter. The same test protocol was used at follow-up until the highest achieved step of the baseline measurement (isoworkload) was reached. Differences in heart rate at the end of the last step between baseline and follow-up measurements were calculated to show changes in exercise capacity.

The submaximal multiple-repetition (X-RM) test procedure on a leg extension machine (EN-Dynamic Leg Extension, Enraf Nonius, Rotterdam, the Netherlands) was used to estimate the maximal strength of the m. quadriceps.[41] Maximal muscle strength was calculated from the maximal number of repetitions at a certain set weight and the Holten diagram.[42]

Maximal isometric strength (N) of the elbow flexors of the dominant arm was measured with the microFET (Biometrics, Almere, the Netherlands), which is a valid and reliable instrument.[43-45] The 'break' method was used to measure the maximal peak force.[43]

Physical training program

After having given written informed consent, the sarcoidosis patients started a 13-week physical training program for one hour, thrice a week. This training program included peripheral muscle training and endurance training.

Peripheral muscle training for both the upper (lateral pull-down, chest press, and triceps dips) and lower (leg press, leg extension, and leg curl) extremities was performed using three sets of eight to ten repetitions, starting at 40% of the calculated multiple-repetition maximum. Each week (three training sessions), the resistance was progressively increased by 3% of the multiple-repetition maximum.

Endurance training consisted of walking on a treadmill, starting at 60% of the maximal walking speed of the 6MWT or cycling on a ergometer starting at 50% Wmax, during 20-30 minutes. Each week (three training sessions), the walking speed or workload on the ergometer was progressively increased by 3% of the maximal assessed walking speed and workload.

The study included low-intensity resistance training and moderate-intensity endurance training, for the following reason.[2] Sarcoidosis patients often suffer from severe physical impairments, such as fatigue, arthralgia and muscle pain, which might

result in a reduced training capacity.[12] A high-intensity training program may worsen these patients' physical complaints, resulting in high dropout rates.

Statistical analysis

Demographic, clinical, and physical data are expressed as mean ± standard deviation (SD) and, where appropriate, in absolute numbers or percentages. Paired samples t-tests were used to test mean differences in continuous data between baseline and follow-up, and nominal data were analyzed using McNemar's test.

P-values <0.05 were considered statistically significant. All analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Twenty-four patients were included in this study. The training program was completed by 18 patients (75%; mean age: 50.3±10.4 years), while six patients dropped out for the following reasons: health problems other than sarcoidosis (n=3), problems with their health insurance (n=2) and stopped without giving a specific reason (n=1). The demographic and clinical characteristics of these patients are summarized in Table 7.1.

At baseline, 16 (89%) patients reported fatigue complaints, 16 (89%) patients had reduced exercise capacity and 14 patients had both.

The mean number of training sessions attended was 29.0±6.8 of the total potential number of 39. No adverse events were recorded during the program. After the training program, 13 (72.2%) patients continued a training program comparable to that used in this study.

Table 7.1 Summary of the demographic and clinical characteristics of the sarcoidosis patients at baseline.

	Total sarcoidosis sample (n=24)	Sarcoidosis participants at baseline (n=18)	Dropouts (n=6)
Demographics			
Females/males	6 / 18	4 / 14	2 / 4
Age (yrs)	49.4 ± 10.5	50.3 ± 10.4	46.7 ± 11.2
Time since diagnosis (yrs)	7.3 ± 7.0	8.1 ± 7.5	4.3 ± 4.2
BMI (kg/m^2)	28.8 ± 4.0	29.3 ± 3.9	27.4 ± 4.2
Medication			
No medication	12	9	3
Prednisone use (yes/no)	7 / 17	6 / 12	1 / 5
Prednisone dosage (mg)	6.8 ± 3.1	6.3 ± 3.1	10.0 ± 0
Methotrexate use (yes/no)	6 / 18	4 / 14	2 / 4
Methotrexate dosage (mg)	10.0 ± 4.2	8.8 ± 4.8	12.5 ± 0
Anti-TNF-α use (yes/no)	3 / 21	1 / 17	2 / 4
Lung function tests			
DLCO (% pred)	88.7 ± 17.9	91.2 ± 18.4	79.4 ± 13.7
FVC (% pred)	100.3 ± 17.5	102.2 ± 18.1	94.7 ± 15.6
FEV_1 (% pred)	93.5 ± 16.9	93.6 ± 17.0	93.3 ± 18.5
Chest radiograph stages			
0 + I / II + III / IV (%)	29.2 / 66.6 / 4.2	27.8 / 66.6 / 5.6	33.3 / 66.7 / 0
Inflammatory markers			
CRP[a]	5.5 ± 6.2	5.4 ± 6.2	6.0 ± 7.0
sIL-2R[b]	3,884 ± 1,918	4,316 ± 1,948	2,417 ± 804
ACE[c]	30.0 ± 11.7	29.2 ± 12.5	32.8 ± 9.4

Data are expressed as mean ± standard deviation (SD) or absolute numbers (n) or percentages (%). BMI: body mass index; TNF: tumor necrosis factor; DLCO: diffusing capacity of the lung for carbon monoxide; % pred: % of predicted value; FVC: forced vital capacity; $FEV_{1:}$ forced expiratory volume in one second; CRP: C-reactive protein; sIL-2R: soluble interleukin-2 receptor, ACE: angiotensin converting enzyme. [a] Normal range <10 mg/l; [b] Normal range 240-3,154 pg/ml; [c] Normal range 12-68 U/l.

Health questionnaires

The results of the health questionnaires are shown in Table 7.2. Patients reported fatigue complaints both at baseline (16; 89%) and after the training program (14; 78%) ($p>0.05$). The mean FAS score had decreased significantly (mean difference -2.7 points, 95% CI -4.4 to -1.1) after the training program (27.0±7.3 points) in comparison with the baseline measurement (29.7±7.7 points). Based on an MCID of 4 points, 6 patients (33.3%) reported reduced, one patient (5.6%) increased and 11 patients (61.1%) stable fatigue complaints after the training program. Based on a 10% change in FAS score, 9 patients (50%) showed reduced, one patient (5.6%) increased and 8 patients (44.4%) stable fatigue complaints after the training program (Table 7.3). Figure 7.1 shows the individual changes in FAS scores between baseline and follow-up measurements.

In addition to the FAS score, the mean score on the psychological health domain of the WHOQOL-BREF and the MRC dyspnea score had improved significantly after the training program. Mean score on the psychological health domain of the WHOQOL-BREF was 13.7±2.6 points at baseline and 14.6±2.6 at follow-up (mean difference 0.9 points, 95% CI 0.2 to 1.7). The mean MRC score showed a significant improvement

at the follow-up measurement (1.6±0.7 points) in comparison with the baseline measurement (2.0±0.7 points; mean difference -0.4 points, 95% CI -0.8 to -0.1).

No significant changes were found in the degree of arthralgia and muscle pain following the training program.

Table 7.2 Differences in questionnaire outcomes of the sarcoidosis patients (n=18) studied before (t0) and after (t1) a training program.

	Sarcoidosis patients t0	Sarcoidosis patients t1	Mean difference in sarcoidosis t1 vs. t0 (95% CI)	p-value
FAS	29.7 ± 7.7	27.0 ± 7.3	-2.7 (-4.4 to -1.1)	0.003
WHOQOL-BREF				
Overall QoL facet	6.2 ± 1.2	6.4 ± 1.8	0.2 (-0.4 to 0.9)	0.48
Physical health	12.7 ± 2.7	13.2 ± 3.1	0.5 (-0.4 to 1.3)	0.24
Psychological health	13.7 ± 2.6	14.6 ± 2.6	0.9 (0.2 to 1.7)	0.02
Social relationships	15.6 ± 2.7	15.5 ± 2.5	-0.1 (-0.7 to 0.4)	0.60
Environment	15.8 ± 2.6	16.1 ± 2.3	0.3 (-0.6 to 1.3)	0.46
MRC	2.0 ± 0.7	1.6 ± 0.7	-0.4 (-0.8 to -0.1)	0.02
VAS				
Joint pain	36.4 ± 26.5	42.2 ± 29.6	5.8 (-3.2 to 14.9)	0.19
Muscle pain	26.8 ± 26.6	36.0 ± 25.8	9.1 (-3.7 to 21.9)	0.15

Data are expressed as mean ± standard deviation (SD). FAS: Fatigue Assessment Scale; WHOQOL-BREF: World Health Organization Quality of Life BREF assessment instrument; QOL: quality of life; MRC: Medical Research Council dyspnea scale; VAS: Visual Analogue Scale.

Table 7.3 Numbers of sarcoidosis patients with changes in FAS scores, 6MWD, and quadriceps muscle strength test results, as a percentage of the baseline value.

	Improvement			Deterioration		
	0-5%	5-10%	≥10%	0-5%	5-10%	≥10%
FAS	2	5	9	1	-	1
6MWD	6	8	3	-	1	-
Quadriceps muscle strength	2	2	12	-	1	1

FAS: Fatigue Assessment Scale; 6MWD: six-minute walking distance.

Physical parameters

The physical test results, measured at baseline and after the training program, are summarized in Table 7.4. In comparison with the baseline measurements (589±88 m) a statistically significant increase in the mean 6MWD of 34.6 m (95% CI 20.3 to 49.0) was seen after completion of the training program (624±92 m). Figure 7.2 shows the individual changes in 6MWD between baseline and follow-up measurement. Seventeen patients showed an increase in 6MWD after the program (<5% increase, n=6; 5-10% increase, n=8; ≥10% increase, n=3; Table 7.3). Heart rate, dyspnea, and leg fatigue severity, measured before and after the 6MWD, had not changed after the training program.

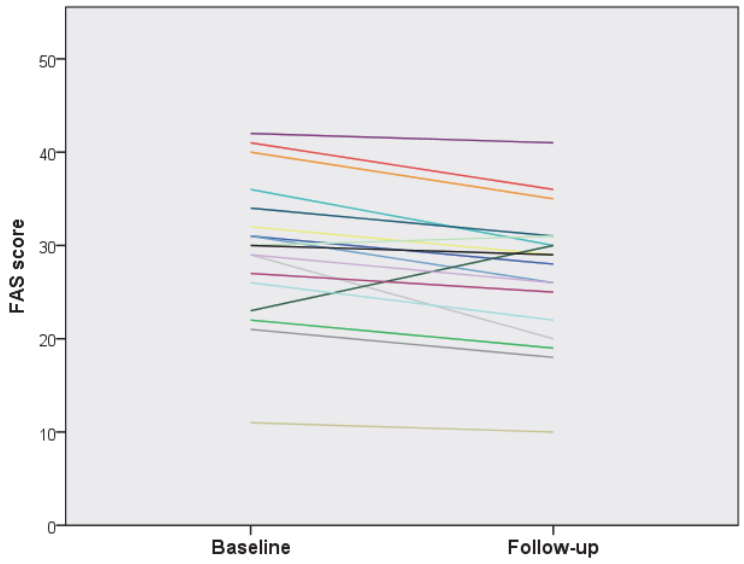

Figure 7.1 Individual changes in fatigue scores, measured with the Fatigue Assessment Scale, following a 13-week physical training program.

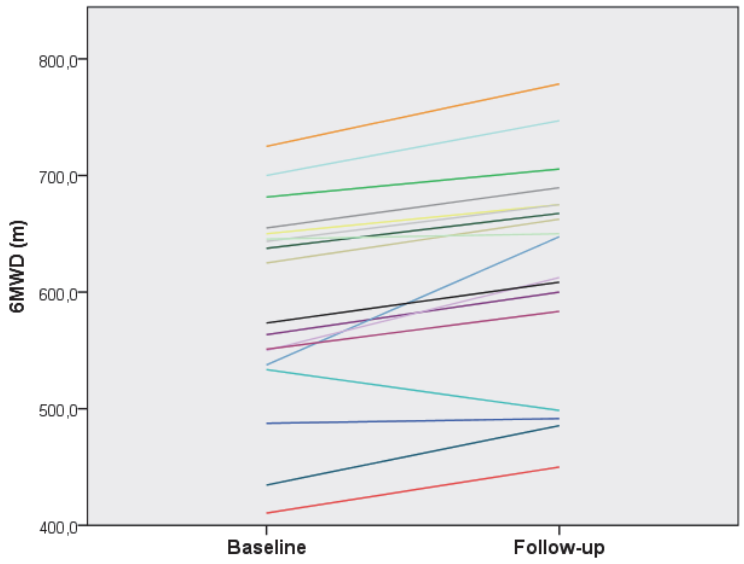

Figure 7.2 Individual changes in six-minute walking distances following a 13-week physical training program.

The submaximal bicycle test was performed at a mean workload of 170.3 Watt (W; range 80-225W). After the training program, the mean heart rate had decreased significantly, by 8.4 beats per minute (95% CI -13.8 to -3.0), going from 146.3±21.5 at baseline to 137.9±19.9 at follow-up.

In contrast to elbow flexor muscle strength, the strength of the quadriceps had improved significantly after the training program, from 48.0±12.5 kg at baseline to 58.7±15.0 kg at follow-up (mean difference 10.7 kg, 95% CI 5.5 to 15.9). Sixteen patients showed an increase in quadriceps muscle strength after the program (<5% increase, n=2; 5-10% increase, n=2; ≥10% increase, n=12; Table 7.3).

Table 7.4 Differences in physical characteristics of the sarcoidosis patients (n=18) studied before (t0) and after (t1) a training program.

	Sarcoidosis patients t0	Sarcoidosis patients t1	Mean difference in sarcoidosis t1 vs. t0 (95% CI)	p-value
Exercise capacity				
6MWD (m)	589 ± 88	624 ± 92	34.6 (20.3 to 49.0)	<0.001
Dyspnea severity, MBS				
Before the 6MWT	0.9 ± 1.2	1.3 ± 1.0	0.3 (-0.2 to 0.9)	0.23
After the 6MWT	2.4 ± 2.0	3.0 ± 2.0	0.6 (-0.4 to 1.6)	0.22
Leg fatigue severity, MBS				
Before the 6MWT	2.0 ± 2.1	1.8 ± 1.4	-0.2 (-1.2 to 0.8)	0.65
After the 6MWT	3.4 ± 2.3	3.2 ± 2.1	-0.3 (-1.0 to 0.5)	0.48
Heart rate (beats per minute)				
Before the 6MWT	82.7 ± 13.1	77.1 ± 12.8	-5.6 (-12.6 to 1.4)	0.11
After the 6MWT	117.6 ± 19.3	118.1 ± 19.0	0.5 (-4.2 to 5.2)	0.83
Bicycle test				
Heart rate (beats per minute)	146.3 ± 21.5	137.9 ± 19.9	-8.4 (-13.8 to -3.0)	0.005
Muscle strength				
Elbow flexors (N)	269.4 ± 76.8	269.9 ± 80.6	0.5 (-19.3 to 20.2)	0.96
Quadriceps (kg)	48.0 ± 12.5	58.7 ± 15.0	10.7 (5.5 to 15.9)	<0.001

Data are expressed as mean ± standard deviation (SD). 6MWD: six-minute walking distance; MBS: modified Borg scale.

Discussion

This pilot study examined changes in fatigue, physical functions, and QoL in fatigued sarcoidosis patients and/or sarcoidosis patients with a reduced exercise capacity, following a 13-week physical training program. The results showed statistically significant improvements in fatigue, the psychological health domain of the WHOQOL-BREF, dyspnea, exercise capacity, and quadriceps muscle strength. No adverse effects or events were reported by the participants during the training period. In general, patient compliance was high and most patients continued a physical training program.

International guidelines state that PR is beneficial for patients with chronic respiratory diseases, regardless of cause.[1] Salhi[46] and Holland *et al*.[47] showed

improvements in fatigue following a training program in patients with restrictive lung diseases (RLD) and ild, respectively. In these studies fatigue was measured with the Chronic Respiratory Disease Questionnaire, whereas the present study used the FAS. The mean FAS score in the present study was significantly reduced, by 2.7 points, while 33.3% and 50.0% of the patients showed reduced fatigue complaints using an MCID of 4 points and 10% change in FAS score, respectively. These results are comparable with those reported by Strookappe *et al*.[6] Furthermore it is conceivable that some patients experienced stable fatigue complaints even though their activity level improved. Unfortunately, the present study did not use an activity monitor (accelerometer) or activity questionnaire, so the activity level could not be related to the fatigue complaints.

The results on the psychological health domain of the WHOQOL-BREF showed a significant improvement of 0.9. Huppmann *et al*.[4] found statistically and clinically significant improvements in health-related QoL in ild patients, including sarcoidosis patients, measured with the SF-36 questionnaire after completing a PR program (PRP), with both the physical and mental health scores of the SF-36 improving. Unfortunately, they did not perform a subgroup analysis for the sarcoidosis patients. Several studies have found significant and clinically relevant improvements in health-related QoL in patients with IPF and COPD after physical training.[5,48-50] However, it is questionable whether these study results can be compared with ours, since the study populations, outcome measures, and training programs differed.

In line with the present study, Holland *et al*.[47] showed reduced dyspnea as measured with the MRC in patients with ild following an 8-week exercise training program, and Ozalevli *et al*.[48] showed reduced dyspnea complaints in patients with IPF. By contrast, Nishiyama *et al*.[5] did not find significant effects of PR on dyspnea. In the present study, the mean perceived dyspnea severity at baseline was already low and therefore not clinically relevant.

Studies have shown that the MCID of the 6MWT for patients with IPF is 24-45 m and for COPD 29-54 m.[36-40] The present study found an improvement in 6MWD of 35 m, which is within the range of the MCID, although at the lower end. Strookappe *et al*.[6] reported a mean improvement on the 6MWT of 51 m following training, and half of their sarcoidosis patients reported an increase of >10%. Holland *et al*.[47] reported improvements in 6MWD (mean 35 m, 95% CI 6-64) in ild patients following an 8-week exercise training program, compared with controls. Huppmann[4] and Nishiyama *et al*.[5] demonstrated improvements in 6MWD of 46 m following a PRP in ild patients, including sarcoidosis patients, and IPF patients, respectively. Several studies have shown improvements in 6MWD in patients with IPF, and Salhi *et al*.[46] even found improvements of 64 m in patients with RLD.[48,49] Kozu *et al*.[50] showed significant improvements in 6MWD in both IPF and COPD patients following an 8-week PRP. However, the magnitude of the improvements was less in patients with IPF.

In line with the present study, Huppmann[4] and Strookappe *et al*.[6] did not find an improvement in dyspnea scores after the 6MWT. However, Ozalevli *et al*.[48] showed a

decrease in perceived dyspnea and leg fatigue at the end of the 6MWT. In general, the mean heart rate and modified Borg score as a measure of dyspnea and leg fatigue severity in our study were low at the end of the 6MWT. The results of our study suggest that the perceived intensity of the 6MWT is acceptable for sarcoidosis patients.

We found a significant reduction in heart rate during the bicycle test, suggesting increased exercise capacity. Holland *et al*.[47] also showed a reduction in heart rate (mean -6.6 beats/minute, 95% CI -11.7 to -1.52) at maximal isoworkload measured during an incremental exercise test following training, indicating cardiovascular adaptation to training.

In contrast to the muscle strength of the elbow flexors, we found significant improvements in muscle strength of the m. quadriceps. This may have been caused by the fact that our training program mainly concentrated on the lower extremity muscles. These results are in line with those reported by Strookappe *et al*.[6] Recent studies have shown that quadriceps strength is correlated to exercise capacity.[13,16,51] Kozu[49,50] and Salhi *et al*.[46] also showed improvements in quadriceps strength in patients with IPF, RLD, and COPD following PR.

Although patients seemed to improve during a 13-week physical training program, improvements were smaller than expected. The duration, frequency, and intensity of an exercise program are critical to achieve physical benefits. The training parameters, duration, and frequency we used are in agreement with international guidelines.[2,52] Training intensity in our study was deliberately chosen to be low to moderate. With hindsight, training with a higher intensity might have yielded greater progression. However, sarcoidosis patients can suffer from various impairments, such as arthralgia, muscle pain, and fatigue, and high-intensity training could worsen these impairments, resulting in high training dropout rates. This is why we used a low to moderate training intensity.

The limited improvements found in this study can also be explained by the heterogeneity of the disease. Disease severity in sarcoidosis is variable, depending on the organs involved, and this variability may have limited the participants' potential to achieve improvements through training.[50] Sarcoidosis patients in our study were physically less impaired than IPF or COPD patients. Perhaps patients with more severe impairments are more likely to show improvements. Ferreira *et al*.[53] showed smaller improvements in 6MWD after PR with increasing baseline 6MWDs.

Study limitations

Our study was subject to some limitations. First, the number of patients included (n=24) was smaller than what was indicated by the sample size calculation (n=34), implying that it was underpowered. Not all sarcoidosis patients with fatigue complaints and/or exercise intolerance who were invited by their pulmonologist to take part actually participated in this study, for various reasons: (1) lack of motivation, (2) participation in another training program, (3) long traveling distance to the training site,

and (4) lack of coverage by their health insurance policy. The exact number of non-participants is unfortunately not known.

This pilot study did not incorporate a control group, so the results have to be interpreted with caution. They cannot show the additional benefits of a training program in comparison with no treatment or usual care. As mentioned in the study by Ferreira *et al*.[53], a pilot study like ours can provide important evidence and suggestions for future studies to stimulate supervised physical training, especially since we found in an earlier study that physical outcome values in sarcoidosis hardly changed during a two-year follow-up study.[15]

Future research

This pilot study showed short-term benefits of a low-intensity physical training program in a small population of sarcoidosis patients. Future research is required to study both the short- and long-term benefits of such a physical training program in a larger sarcoidosis population, preferably using a randomized clinical trial design. The long-term benefits of a physical training program in sarcoidosis are still unknown. Furthermore, the intensity of the training should be optimized; improvements may be more obvious following a high-intensity training. Finally, the additional benefits of multidisciplinary PR should also be studied. The present study examined changes in physical functions following a monodisciplinary physical training program supervised by a physical therapist. Besides physical training, a multidisciplinary PR may include education and behavior change to improve the physical and psychological condition of people with chronic respiratory disease and to promote disease management.[1]

In conclusion, fatigue reduced after a period of physical training in sarcoidosis patients. Moreover, psychological health and physical functions improved. This physical training was safe for patients with sarcoidosis. Future studies are warranted to assess the benefits of physical training in sarcoidosis.

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