Chapter 4

Exercise capacity, muscle strength, and fatigue in sarcoidosis: a follow-up study

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Abstract

Purpose

The purpose of this study was to examine changes in the prevalence of exercise intolerance, reduced muscle strength, and fatigue and the changes in these parameters in individual patients during a 2-year follow-up study.

Methods

Ninety sarcoidosis patients (62 males and 28 females; mean age: 46.0±10.2 years) participated in a 2-year follow-up study. At the baseline and follow-up measurements, patients performed a 6-minute walk test and elbow flexor muscle strength, quadriceps peak torque, and hamstrings peak torque tests. Maximal inspiratory pressure was recorded. All patients completed the Fatigue Assessment Scale.

Results

Both at baseline and follow-up, a substantial proportion of the patients showed a reduced 6-minute walk test (41.6% and 34.8%, respectively), elbow flexor muscle strength (6.7% and 14.6%), quadriceps peak torque (21.3% and 18.0%), hamstrings peak torque (13.5% and 12.4%), and maximal inspiratory pressure (45.9% and 48.6%). The majority of the patients reported fatigue (86% and 77%). These physical impairments remained stable during the follow-up period. The prevalence of these physical impairments in patients diagnosed with sarcoidosis <2 years before inclusion in this study was similar to that in patients with a longer history of the disease.

Conclusions

Exercise intolerance, muscle weakness, and fatigue are frequent problems in symptomatic sarcoidosis patients with a stable and persistent character. This study highlights that beyond medical treatment a rehabilitation program should be considered as adjunct therapy in the multidisciplinary management of sarcoidosis patients even though the achieved benefit needs future studies.

Introduction

The course of sarcoidosis is unpredictable and clinical manifestations are variable, depending on the organs involved.[1-3] Patients consult their physician not only with organ-specific symptoms, but also with nonspecific health complaints, such as fatigue, exercise intolerance, and muscle weakness.[4] These physical impairments in sarcoidosis are disabling, especially when they become chronic.[5,6] Nearly two-thirds of sarcoidosis patients may show spontaneous remission in the first two years after diagnosis. Nevertheless, sarcoidosis is reported to become chronic (>2 years) or progressive in 10-30%.[1,2] There are currently no data about the course of physical complaints and fatigue in these subgroups of sarcoidosis patients.

Fatigue is the most frequently reported symptom in sarcoidosis, with a prevalence of 60-90%.[5,7,8] In the study by Marcellis *et al*.[9], 81% of the sarcoidosis patients in the sample reported fatigue and 26% of the fatigued patients reported extreme fatigue. This study[9] also found exercise intolerance and muscle weakness to be frequent problems in sarcoidosis, both in fatigued and nonfatigued patients. Previous studies also found reduced 6-minute walking distances (6MWDs) and/or muscle weakness in sarcoidosis.[10-15]

So far, only cross-sectional designs have been used to study the prevalence of exercise intolerance, muscle weakness, and fatigue in sarcoidosis, and studies using a longitudinal design are lacking. No conclusions therefore can be drawn with regard to changes in these physical parameters over time in sarcoidosis.

Another question is whether patients diagnosed with sarcoidosis <2 years ago show remission of the physical complaints in the first two years after diagnosis and whether it is true that 10-30% develop chronic physical complaints. These points are obviously of clinical interest in the management of sarcoidosis patients, as a rehabilitation program could offer added value in patients with persistent physical complaints.[13,16]

The purpose of the current study was to examine changes in the prevalence of exercise intolerance, reduced muscle strength, and fatigue and to assess the changes in these parameters in individual patients during a 2-year follow-up study.

Methods

Subjects

Between November 2008 and September 2009, 124 symptomatic sarcoidosis patients referred to the interstitial lung disease (ild) care team of the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC; the Netherlands) were included in a cross-sectional study.[9] Patients were diagnosed with sarcoidosis according to the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines.[1] Between July 2010 and September 2011, all participants of the 2008/9

study[9] living in the southern part of the Netherlands (n=104) were invited to participate in the follow-up measurement.

Measurements

All measurements in this study have been described previously.[9] Both at baseline and follow-up, the data were collected between 10:30 and 14:00. The physical test results and fatigue scores of the 2008/9 cross-sectional study were used as baseline values.[9] During the 2008/9 cross-sectional study a healthy control group (n=62) matched for age and sex was recruited from hospital employees and the surrounding community (Table 4.1).

Table 4.1 Summary of the demographic and clinical characteristics of the sarcoidosis patients studied at baseline and follow-up and the healthy controls.

	Total sarcoidosis sample 2008-2009	Sarcoidosis patients at baseline	Sarcoidosis patients at follow-up	Dropouts	Healthy controls
Demographics					
Subjects	124	90	90	34	62
Females/males	44 / 80	28 / 62	28 / 62	16 / 18	22 / 40
Age (yrs)	46.6 ± 10.2	46.0 ± 10.2	47.8 ± 10.2	48.5 ± 10.2	46.4 ± 9.9
Time since diagnosis (yrs)	6.1 ± 6.2	5.9 ± 5.8		6.6 ± 7.0	NA
BMI (kg/m^2)	28.0 ± 4.7	28.5 ± 4.6	28.4 ± 4.6	26.7 ± 4.5	24.7 ± 1.8
Nonsmokers/smokers	113 / 11	83 / 7	83 / 7	30 / 4	56 / 6
Medication					
No medication	76	54	57	22	62
Prednisone use (yes/no)	48 / 76	36 / 54	32 / 58	12 / 22	0 / 62
Prednisone dosage (mg)	13.2 ± 7.4	11.8 ± 5.6	8.3 ± 3.5[c]	14.6 ± 8.9	0
Methotrexate use (yes/no)	39 / 85	29 / 61	33 / 57	10 / 24	0 / 62
Methotrexate dosage (mg)	10.8 ± 3.1	10.1 ± 2.8	9.6 ± 3.3	10.8 ± 4.3	0
Anti-TNF-α use (yes/no)	14 / 110	13 / 77	21 / 69[c]	1 / 33	0 / 62
Lung function tests					
DLCO (% pred)	75.7 ± 17.6	76.6 ± 17.4	77.0 ± 17.9	71.1 ± 19.3	NA
FVC (% pred)	98.3 ± 20.8	98.5 ± 19.6	99.0 ± 17.9	95.7 ± 23.9	NA
FEV_1 (% pred)	84.2 ± 22.6	84.6 ± 21.7	85.4 ± 22.0	78.0 ± 25.1	NA
Chest radiograph stages					
0 + I/II + III/IV (%)	37 / 37 / 26	39 / 38 / 23	41 / 36 / 23	31 / 38 / 31	NA
Inflammatory markers					
CRP[a]	8.6 ± 15.4	8.0 ± 12.6	3.8 ± 3.6[c]	9.4 ± 16.9	NA
sIL-2R[b]	3,282 ± 2,331	2,995 ± 1,501	2,366 ± 1,505[c]	3,578 ± 2,440	NA
Fatigue measure					
FAS score	28.3 ± 7.7	28.6 ± 7.2	26.5 ± 7.2[c]	27.4 ± 8.8	15.6 ± 4.0
WHOQOL-BREF					
Overall QoL facet	5.9 ± 1.6	5.9 ± 1.5	6.3 ± 1.6[c]	6.0 ± 1.8	8.7 ± 1.0
Physical health domain	12.3 ± 2.8	12.4 ± 2.8	13.3 ± 2.8[c]	12.1 ± 3.0	17.9 ± 1.5

Data are expressed as mean ± standard deviation (SD) or absolute numbers (n). 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; FAS: Fatigue Assessment Scale; WHOQOL-BREF: World Health Organization Quality of Life-BREF assessment instrument; QoL: quality of life; NA: not applicable. [a] Normal range <10 mg/l; [b] Normal range 240-3,154 pg/ml; Sarcoidosis patients (n=90) at baseline versus follow-up: [c] $p<0.05$.

These data were used as reference values for exercise capacity and peripheral muscle strength results for both the baseline and follow-up measurements (Tables 4.2, 4.3).[9]

This study was approved by the local Medical Ethics Committee of the MUMC. Written, informed consent was obtained from all participants.

Table 4.2 Summary of the physical characteristics of the male sarcoidosis patients studied at baseline (t0) and follow-up (t1) and the male healthy controls.

Males (n=62)	Sarcoidosis patients t0	Sarcoidosis patients t1	Controls (n=40)	Mean difference sarcoidosis t1 vs. t0 (95% CI)	Mean difference controls vs. sarcoidosis t0 (95% CI)	Mean difference controls vs. sarcoidosis t1 (95% CI)
Exercise capacity						
6MWD (m)	609 ± 93	627 ± 98	747 ± 74	18.4 (4.6 to 32.2)[a]	138.8 (104.2 to 173.4)[b]	120.4 (86.5 to 154.3)[b]
6MWD (% pred)	81.4 ± 12.4	83.9 ± 13		2.5 (0.6 to 4.3)[a]		
Muscle force						
EFMS (N)	257.4 ± 54.8	247.0 ± 67.0	287.0 ± 47.9	-10.4 (-21.7 to 0.9)	29.6 (8.6 to 50.6)[a]	40.0 (15.7 to 64.3)[a]
EFMS (% pred)	89.7 ± 19.1	86.1 ± 23.4		-3.6 (-7.5 to 0.3)		
QPT (Nm)	96.6 ± 30.5	99.2 ± 31.1	118.4 ± 23.0	2.7 (-3.0 to 8.3)	21.9 (10.7 to 33.1)[b]	18.8 (8.1 to 29.4)[a]
QPT (% pred)	81.6 ± 25.7	83.8 ± 26.3		2.2 (-2.5 to 7.0)		
HPT (Nm)	70.7 ± 23.2	72.1 ± 23.1	86.3 ± 18.7	1.4 (-2.3 to 5.1)	15.6 (6.9 to 24.3)[a]	13.8 (5.2 to 22.5)[a]
HPT (% pred)	82.0 ± 26.9	83.6 ± 26.7		1.6 (-2.7 to 5.9)		
PImax (% pred)	79.3 ± 25.8	83.3 ± 24.4	NA	4.0 (-0.4 to 8.4)	NA	NA

Data are expressed as mean ± standard deviation (SD). 6MWD: 6-minute walking distance; % pred: % of predicted value; EFMS: elbow flexor muscle strength; QPT and HPT: isokinetic quadriceps and hamstrings peak torques at 180° per second; PImax: maximal inspiratory pressure, NA: not applicable. [a] $p<0.05$; [b] $p<0.001$.

Clinical data

Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the diffusing capacity of the lung for carbon monoxide (DLCO) were measured.[17] Chest radiographs were graded according to the radiographic staging proposed by DeRemee.[1]

The C-reactive protein (CRP) concentration and the serum levels of soluble interleukin-2 receptor (sIL-2R) were analyzed.[18] According to performed validations and the manufactory's instructions the repeatability coefficient of variation (CV) and the intermediate precision CV for CRP measurements are 3% and 4%, respectively, and for sIL-2R measurements 8% and 5% respectively.

Table 4.3 Summary of the physical characteristics of the female sarcoidosis patients studied at baseline (t0) and follow-up (t1) and the female healthy controls.

Females (n=28)	Sarcoidosis patients t0	Sarcoidosis patients t1	Controls (n=22)	Mean difference sarcoidosis t1 vs. t0 (95% CI)	Mean difference controls vs. sarcoidosis t0 (95% CI)	Mean difference controls vs. sarcoidosis t1 (95% CI)
Exercise capacity						
6MWD (m)	553 ± 87	572 ± 85	679 ± 73	18.3 (-2.3 to 39.0)	128.8 (82.2 to 175.5)[b]	107.3 (61.2 to 153.3)[b]
6MWD (% pred)	81.5 ± 12.8	84.2 ± 12.4		2.7 (-0.4 to 5.8)		
Muscle force						
EFMS (N)	160.0 ± 27.1	162.6 ± 34.3	162.6 ± 22.9	2.6 (-6.6 to 11.8)	2.6 (-12.0 to 17.2)	1.9 (-15.5 to 19.3)
EFMS (% pred)	98.4 ± 16.7	100.0 ± 21.1		1.6 (-4.1 to 7.3)		
QPT (Nm)	60.0 ± 19.9	65.7 ± 19.9	70.2 ± 13.3	5.7 (2.1 to 9.2)[a]	10.2 (0.3 to 20.1)[a]	4.5 (-4.9 to 14.0)
QPT (% pred)	85.5 ± 28.4	93.6 ± 28.3		8.1 (3.0 to 13.1)[a]		
HPT (Nm)	48.2 ± 16.2	48.5 ± 12.8	55.3 ± 15.3	0.2 (-3.9 to 4.3)	7.1 (-2.0 to 16.1)	6.9 (-1.1 to 14.9)
HPT (% pred)	87.2 ± 29.3	87.6 ± 23.2		0.4 (-7.0 to 7.8)		
PImax (% pred)	87.1 ± 33.4	85.2 ± 28.8	NA	-1.9 (-13.0 to 9.1)	NA	NA

Data are expressed as mean ± standard deviation (SD). 6MWD: 6-minute walking distance; % pred: % of predicted value; EFMS: elbow flexor muscle strength; QPT and HPT: isokinetic quadriceps and hamstrings peak torques at 180° per second; PImax: maximal inspiratory pressure; NA: not applicable. [a] $p<0.05$; [b] $p<0.001$.

Exercise capacity and muscle strength

The 6-minute walk test (6MWT) was used to assess exercise capacity and performed according to the American Thoracic Society guidelines.[19] The 6MWT is a reliable measure of exercise capacity in patients with pulmonary and cardiac diseases.[20,21]

The Biodex System 3 Pro dynamometer was used to measure isokinetic peak torques (in Nm) of the hamstrings and quadriceps, with a velocity of 180°/second.[22] The Biodex is a reliable and valid isokinetic dynamometer.[23,24]

Maximal isometric strength (in Newton) of the elbow flexors was measured with the microFET.[25] This hand-held dynamometer is a reliable instrument.[25,26] Maximal inspiratory pressure (PImax) was assessed by measuring maximal respiratory mouth pressures.[27]

Questionnaires

Fatigue was measured with the Fatigue Assessment Scale (FAS).[28] FAS scores <22 indicate no fatigue. The minimal clinically important difference (MCID) of the FAS in

sarcoidosis patients is a 4-point or 10% change in FAS score.[28,29] The psychometric properties of the FAS also are good in sarcoidosis.[30]

The World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF) is a measure of quality of life (QoL). It consists of 24 questions in four domains (physical health, psychological health, social relationships, and environment) and two questions that compose the overall QoL and general health facets.[31]

Statistical analysis

Data are expressed as mean ± standard deviation (SD) and, if appropriate, in absolute numbers or percentages. Paired sample t-tests were used to test mean differences in continuous data of the patient group at baseline, and follow-up and nominal data were analyzed using Chi-square. To detect differences between the patient and control groups, continuous data were analyzed with independent sample t-tests and nominal data were tested using Chi-square tests.

Physical test results below the mean values of the control group minus two times SD (95% confidence interval) were assumed to indicate exercise intolerance or muscle strength impairment. The cutoff value for PImax, FVC, FEV_1, and DLCO was <80% of the predicted value.[17,32] Frequency distributions were used to determine the prevalence of exercise intolerance, reduced muscle strength, and fatigue. Symmetry and changes in prevalence rates between the baseline and follow-up physical tests were analyzed by means of crosstabs and Chi-square tests.

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

In total, 104 participants of the 2008/9 study were invited to participate in the follow-up study. Fourteen of these patients were unable to participate, for the following reasons: death (n=2), exacerbations of sarcoidosis (n=2), health problems other than sarcoidosis (n=4), and change of address without notice (n=6). Finally, 90 patients (mean follow-up: 1.9±0.4 years) participated. The clinical data of the patients at baseline and follow-up are summarized in Table 4.1. Most patients (n=75) did not participate in a rehabilitation program during this study. Only six patients started, three stopped, and six patients continued their rehabilitation program during the follow-up period.

No differences in demographic, clinical, or physical characteristics were found between the patients who dropped out and those remaining in the study. We therefore regarded the patients who participated in the follow-up study as a randomly selected group of the patients studied in 2008-9 (Table 4.1).

Exercise capacity

Sarcoidosis patients showed a significantly lower 6MWD (Tables 4.2, 4.3) and a higher prevalence of reduced exercise capacity compared with healthy controls both at baseline and follow-up.

Virtually no difference in mean 6MWD was found between the baseline and follow-up measurements (Tables 4.2, 4.3). Exercise capacity was reduced (relative to the control group) in 41.6% and 34.8% of the total population at the baseline and follow-up measurements, respectively. The prevalence of reduced exercise capacity at follow-up was higher in male sarcoidosis patients. The measurements at baseline and follow-up were highly related (Tables 4.4, 4.5). Figure 4.1 also shows this high level of agreement ($r=0.83$; $p<0.001$) in 6MWD between the baseline and follow-up measurement.

Table 4.4 Prevalence of reduced (i.e., lower than predicted) physical test values at baseline and follow-up of the sarcoidosis patients studied.

	Prevalence of reduced physical test values at baseline (%)	Prevalence of reduced physical test values at follow-up (%)	Chi-square test (p-value)
Total sarcoidosis sample			
6MWD (% reduced)	41.6	34.8	<0.001
EFMS (% reduced)	6.7	14.6	0.011
QPT (% reduced)	21.3	18.0	<0.001
HPT (% reduced)	13.5	12.4	0.018
PImax (% reduced)	45.9	48.6	<0.001
Male sarcoidosis patients			
6MWD (% reduced)	41.9	38.7	<0.001
EFMS (% reduced)	4.8	19.4	0.033
QPT (% reduced)	19.7	21.3	<0.001
HPT (% reduced)	16.4	16.4	0.027
PImax (% reduced)	45.1	49.0	<0.001
Female sarcoidosis patients			
6MWD (% reduced)	40.7	25.9	0.005
EFMS (% reduced)	11.1	3.7	0.004
QPT (% reduced)	25.0	10.7	0.001
HPT (% reduced)	7.1	3.6	0.778
PImax (% reduced)	47.8	47.8	0.022

Data are expressed as percentages (%). 6MWD: 6-minute walking distance; EFMS: elbow flexor muscle strength; QPT and HPT: isokinetic quadriceps and hamstrings peak torques at 180° per second; PImax: maximal inspiratory pressure.

Muscle strength

All mean peripheral muscle strength test results were significantly lower in male sarcoidosis patients compared with the control subjects (Table 4.2). In contrast to these findings, hardly any differences in mean test results were found between female sarcoidosis patients and healthy controls (Table 4.3).

Table 4.5 Crosstab showing the numbers of sarcoidosis patients with a normal and reduced 6-minute walking distance at the baseline and follow-up measurements.

		Follow-up measurement		
		Reduced 6MWD	Normal 6MWD	
Baseline measurement	Reduced 6MWD	27	10	37
	Normal 6MWD	4	48	52
		31	58	89

Data are expressed as absolute numbers. 6MWD: 6-minute walking distance.

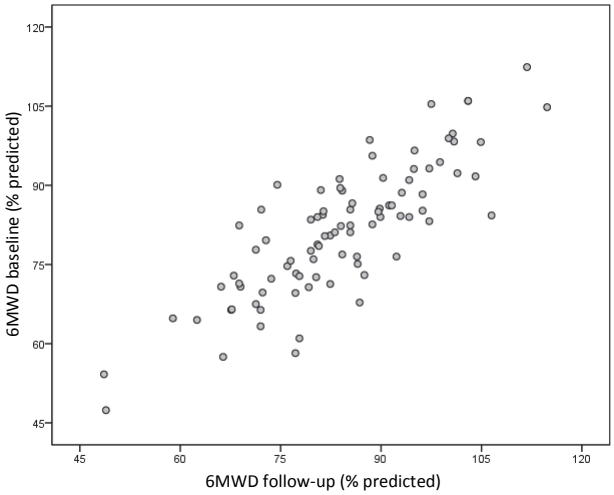

Figure 4.1 Correlation between the 6-minute walking distance (6MWD) as a percentage of the predicted value measured at baseline and the 6MWD as a percentage of the predicted value measured at follow-up in patients with sarcoidosis (r=0.830; p<0.001).

Although female sarcoidosis patients showed a small, yet statistically significant improvement of the quadriceps peak torques at the follow-up measurement compared with the baseline measurement (p=0.003), none of the other mean peripheral muscle strength test results appeared to be changed neither for men nor for women (Tables 4.2, 4.3). Both at baseline and follow-up, a substantial proportion of the sarcoidosis patients showed reduced elbow flexor muscle strength (6.7% and 14.6%, respectively), quadriceps (21.3% and 18.0%, respectively; Table 4.6; Figure 4.2) and hamstrings (13.5% and 12.4%, respectively) peak torques, and PImax (45.9% and 48.6%, respectively; Table 4.4). In general, male sarcoidosis patients showed higher prevalences of reduced muscle strength. Table 4.4 also shows a high level of agreement in test results between the baseline and follow-up measurements of the peripheral muscle strength tests.

During the follow-up period in four cases the prednisone was stopped, and in 20 cases the dose was tapered. In four cases methotrexate (MTX) was started.

However, in most cases the treatment at inclusion was continued with only a small dose adaption due to the chronicity of the disease. In this study, eight patients started anti-TNF-α treatment during the follow-up period (Table 4.1). Neither exercise capacity nor muscle strength was found to be related to medication use (prednisone, methotrexate, and anti-TNF-α) and participation in a rehabilitation program.

Table 4.6 Crosstab showing the numbers of sarcoidosis patients with normal and reduced isokinetic peak torques of the quadriceps at the baseline and follow-up measurements.

		Follow-up measurement		
		Reduced QPT	Normal QPT	
Baseline measurement	Reduced QPT	10	9	19
	Normal QPT	6	64	70
		16	73	89

Data are expressed as absolute numbers. QPT: isokinetic quadriceps peak torques at 180° per second.

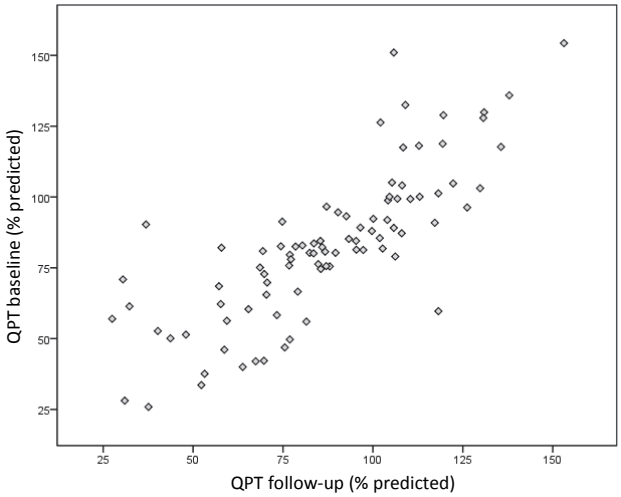

Figure 4.2 Correlation between the quadriceps peak torque (QPT) as a percentage of the predicted value measured at baseline and the QPT as a percentage of the predicted value measured at follow-up ($r=0.794$; $p<0.001$) in patients with sarcoidosis.

Fatigue

Although the difference in mean FAS score was small between baseline and follow-up measurements in our sarcoidosis patients, it was statistically significant (Table 4.1). The prevalences of fatigue in sarcoidosis at baseline and follow-up were 86% and 77%, respectively. Of these fatigued patients, 23% reported extreme fatigue at baseline and 14% at follow-up (Chi-square test: $p=0.048$). There was a significant relationship between these paired measurements (Chi-square test: $p=0.012$). The mean FAS score

(15.6±4.0) and the prevalence of fatigue (4.8%) were significantly lower in the control group than among the sarcoidosis patients ($p<0.001$).

Based on the MCID of the FAS (4 points difference), fatigue complaints were reduced, increased, or stable at the follow-up measurement in 31, 10, and 49 patients, respectively. When we used a 10% change in FAS score as MCID, fatigue complaints were reduced, increased, or stable at the follow-up measurement in 36, 16, and 38 patients, respectively. Analysis of these subgroups showed no differences between them regarding demographic characteristics (age, sex, time since diagnosis), lung function test results (DLCO% pred, FVC% pred, and FEV_1% pred), levels of inflammatory markers (CRP and sIL-2R), radiographic stages, medication use (prednisone, methotrexate, and anti-TNF-α), exercise capacity (Figure 4.3) or muscle strength. The only difference was that the subgroup that reported a reduction in fatigue included more patients started anti-TNF-α treatment than the other subgroups.

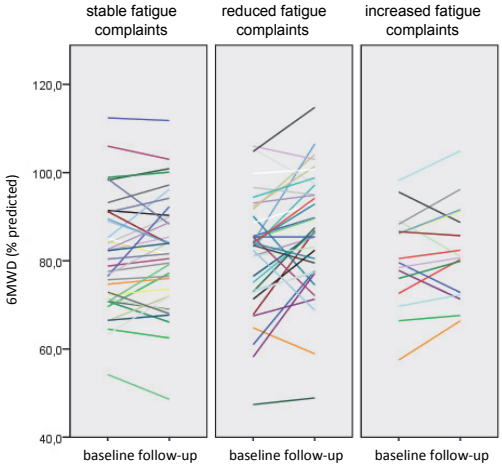

Figure 4.3 Individual changes in 6-minute walking distance (6MWD) as a percentage of the predicted value of the sarcoidosis patients studied, stratified by stable (n=38), reduced (n=36), or increased (n=16) fatigue complaints (MCID: 10% difference on the Fatigue Assessment Scale (FAS)).

Time since diagnosis

Our evaluation of the total population revealed no differences in physical test results or FAS scores between the baseline and follow-up measurements. Evaluation of two subgroups, i.e., patients who were diagnosed with sarcoidosis <2 years before inclusion in this study and those with a history of sarcoidosis of more than two years did not reveal any differences. This subgroup analysis showed no differences in physical test results or FAS scores between the baseline and follow-up measurements.

Discussion

To the best of our knowledge, this is the first longitudinal study in sarcoidosis to examine changes in exercise capacity, muscle strength, and fatigue at group and individual level over a 2-year period. So far, only cross-sectional study designs had been used to assess the prevalence of these physical impairments in sarcoidosis, which meant that no conclusions could be drawn with regard to the progression of the disease severity. This longitudinal study demonstrated that exercise intolerance, muscle weakness, and fatigue are frequent problems in sarcoidosis patients and that these physical impairments persisted over a 2-year follow-up period. These physical impairments appeared to be similar for patients diagnosed with sarcoidosis <2 years before inclusion in this study and those with a longer disease history.

Exercise capacity

In the present study, exercise capacity was reduced in 41.6% of the patients at baseline and in 34.8% at follow-up. Exercise intolerance in sarcoidosis has been reported in several cross-sectional studies. In line with the present study, Spruit *et al*.[13] found reduced 6MWD in fatigued sarcoidosis patients and Kabitz *et al*.[12] in male sarcoidosis patients. Alhamad *et al*.[10] and Baughman *et al*.[11] even reported a 6MWD of <400 m in 73% and 51% of their respective sarcoidosis populations. The differences in 6MWD findings between these studies might be explained by gender and ethnicity. Several studies found that female gender was associated with a reduced 6MWD.[9-11] Al-Nozha *et al*.[33] reported a high prevalence of inactivity among Saudi adults, leading to physical deconditioning. In contrast to the findings reported in the literature[1,2], our subgroup analysis showed that physical impairments in patients diagnosed with sarcoidosis <2 years before inclusion in this study mostly remained unchanged during the 2-year follow-up period.

Muscle strength

In the present study, a substantial proportion of the sarcoidosis patients showed reduced peripheral muscle strength, i.e., elbow flexor muscle strength (6.7% and 14.6%), quadriceps (21.3% and 18.0%), and hamstrings (13.5% and 12.4%) peak torques and PImax (45.9% and 48.6%) at the baseline and follow-up measurements, respectively. Reduced quadriceps peak torques in sarcoidosis patients also were reported by Spruit *et al*.[13] Inspiratory muscle weakness in sarcoidosis also has been reported in several studies.[12-15]

Although the sample size of female sarcoidosis patients in the present study was rather small, we found a tendency toward more physical impairments in male compared with female sarcoidosis patients. In general, male sarcoidosis patients showed more reduced lung function values (FEV_1 and FVC) and suffered from more severe pulmonary sarcoidosis according to the chest X-ray stages.

In line with other studies, we found a relationship between exercise capacity and both the quadriceps and hamstrings muscle strength in sarcoidosis patients.[13] In a study by Miller *et al*.[34], 67% of the sarcoidosis patients terminated their peak exercise test because of "leg complaints", which was considered an indication of skeletal muscle weakness. There are several reasons why muscle weakness develops in sarcoidosis, including sarcoid granuloma infiltration in the muscles, steroid-induced myopathy, increased circulating inflammatory markers, and physical deconditioning. Sarcoid muscle involvement is mostly asymptomatic and therefore an underdetected problem. Symptomatic muscle involvement is rare in sarcoidosis. Corticosteroid treatment is indicated in this latter group, often resulting in improved muscle functions.[35] However, no muscle biopsies were performed in the present study. Quadriceps muscle strength has been found to be inversely related to the daily dose of corticosteroids in fatigued sarcoidosis patients.[13] Although corticosteroids are known to cause a myopathy, Spruit *et al*.[13] found no differences in muscle strength between patients using corticosteroids and those who did not. In line with this, the present study and a previous study by Marcellis *et al*.[9] did not find an association between muscle strength and prednisone dosage either. The effects of corticosteroid treatment on muscle strength in sarcoidosis thus remain unclear.

Sarcoidosis patients have been found to exhibit higher plasma TNF-α concentrations than control subjects.[28] Elevated TNF-α levels may cause muscle dysfunction in chronic diseases. Although the median circulating level of TNF-α was higher in sarcoidosis patients compared with healthy controls, TNF-α did not correlate with muscle strength.[13]

According to the present study, fatigue, exercise intolerance, and muscle weakness are frequent reported symptoms in sarcoidosis. These disabling symptoms may cause physical inactivity in sarcoidosis, resulting in general deconditioning. In turn, general deconditioning may cause more perceived fatigue, physical impairments, and a reduction in daily activities. This is called the negative vicious circle of physical deconditioning.[13] However, the degree of physical inactivity was not measured in the present study, because this was beyond the scope of this study.

Fatigue

The etiology of fatigue seems to be multifactorial but remains unclear.[4,9,28] In the present study, the prevalence of fatigue at baseline was 86% and at follow-up 77%, which is in line with previous studies.[5,9,11,36] Sarcoidosis mostly affects young adults. Fatigue and physical impairments can obviously have a major influence on the daily activities, social, and working lives of these patients, resulting in a reduced QoL.[5]

Although the differences we found in fatigue complaints and QoL were statistically significant, they may be (clinically) irrelevant from the patients' point of view. A study by de Kleijn *et al*.[29] showed that a change in FAS score over time of at least four points represents the MCID. Recently, Drent *et al*.[28] established a percentage-based MCID in the FAS score of 10%. Regardless of whether we used a four-point or a 10% MCID[28,29],

our subgroup analysis showed no differences in demographic, clinical, or physical characteristics between patients with stable, reduced, or increased fatigue complaints. The only difference was that the subgroup of patients who demonstrated a clinically relevant improvement in terms of fatigue included more patients who had started anti-TNF-α treatment during the follow-up period.

In general, physicians assess disease severity and progression in sarcoidosis on the basis of clinical test results, such as pulmonary function tests, chest radiographs, and serological tests. However, these objective clinical parameters correlate poorly with the patients' subjective feeling of well-being.[7] For example, fatigue and general weakness may persist even if routine clinical tests results have returned to normal.[5,7] Assessment of the presence of physical impairments provides additional information about the patient's functional status, disease severity, and progression.[6,37] Therefore, we recommend physical tests in the multidisciplinary management of sarcoidosis. Huppmann *et al*.[38] demonstrated in a large cohort of patients with ild, including sarcoidosis patients (n=50), that pulmonary rehabilitation (PR) had a positive impact on functional status and QoL. They concluded that PR appears to be a valuable adjunct therapy in patients with ild, including sarcoidosis. Therefore, a rehabilitation program should be considered in those patients with persistent or progressive physical impairment.

Study limitations

At baseline, this study included refractory sarcoidosis patients suffering from severe physical complaints referred to a tertiary clinic, which may have caused selection bias. Because this selection may have resulted in an overestimation of the prevalence of reduced exercise capacity, muscle weakness, and fatigue, these results may not be valid for all sarcoidosis patients.

The physical tests performed in this study are volitional tests, and the results partially depend on the patient's motivation and cooperation. Nonvolitional testing would possibly yield more valid results. However, the used tests are generally accepted in clinical studies[13], and in our experience, sarcoidosis patients are very cooperative and motivated to participate in research projects.

Future research

This study was not designed to answer the question why some patients show improvements in terms of physical impairments while others report progression of disease severity. Future research should include prospective intervention studies to explore the relationship between physical impairments and different treatment strategies in sarcoidosis. In addition to medication, exercise training in patients with sarcoidosis should be considered, because it has been shown to be effective in treating exercise intolerance, muscle weakness, and fatigue in several chronic diseases, including sarcoidosis.[38,39]

We conclude that exercise intolerance, muscle weakness, and fatigue are frequent problems in sarcoidosis patients and that these complaints may last for considerable periods of time. In patients with a physical impairment a rehabilitation program should be considered as adjunct therapy, even though the achieved benefit needs future studies.

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