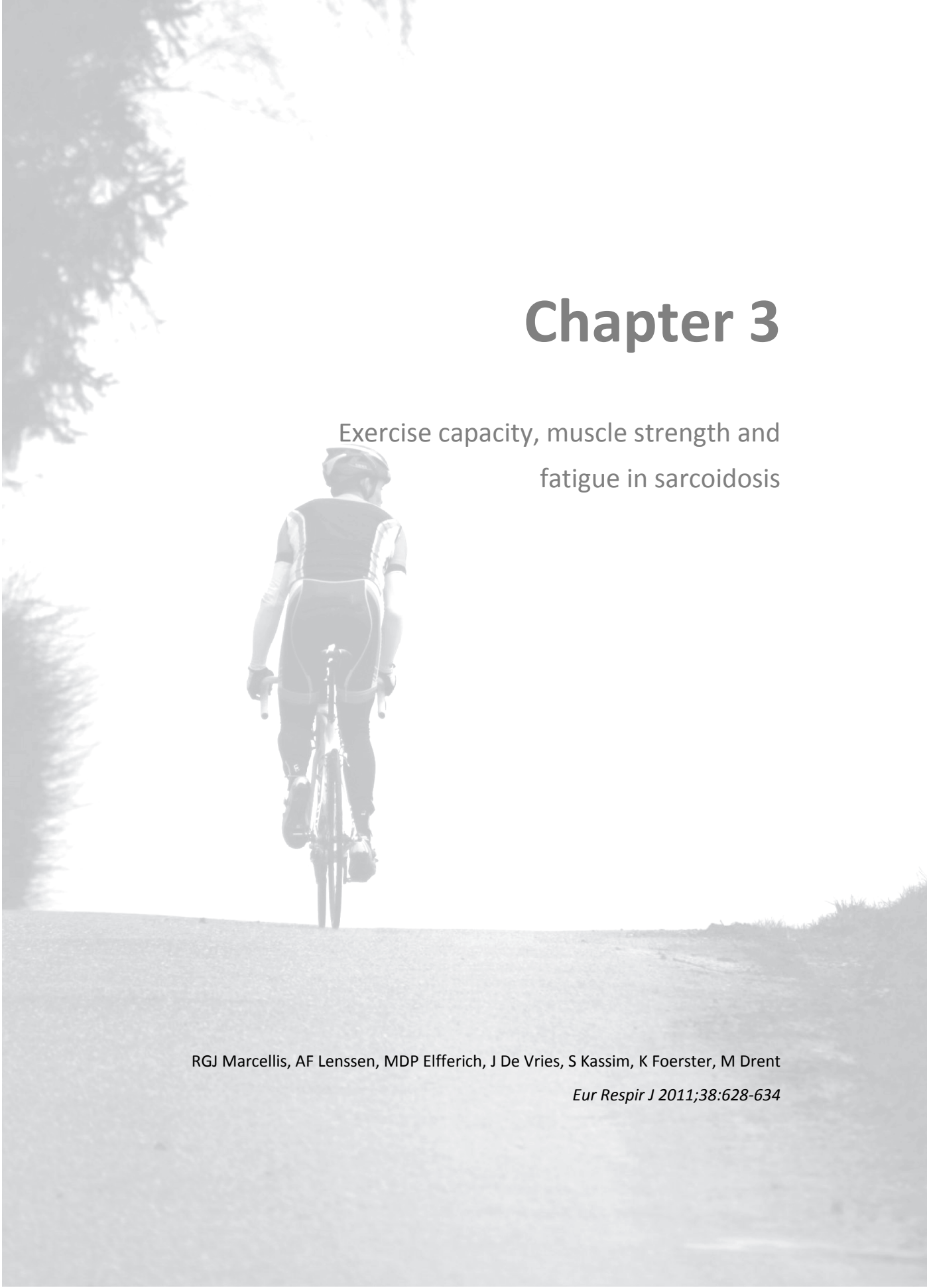

Chapter 3

Exercise capacity, muscle strength and fatigue in sarcoidosis

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Abstract

Aims

The aim of this case-control study was to investigate the prevalence of exercise intolerance, muscle weakness and fatigue in sarcoidosis patients. Additionally, we evaluated whether fatigue can be explained by exercise capacity, muscle strength or other clinical characteristics (lung function tests, radiographic stages, prednisone usage and inflammatory markers).

Methods

One hundred twenty-four sarcoidosis patients (80 males) referred to the Maastricht University Medical Centre (Maastricht, the Netherlands) were included (mean age 46.6±10.2 yrs). Patients performed a 6-minute walk test (6MWT) and handgrip force (HGF), elbow flexor muscle strength (EFMS), quadriceps peak torque (QPT) and hamstring peak torque (HPT) tests. Maximal inspiratory pressure (PImax) was recorded. All patients completed the Fatigue Assessment Scale (FAS) questionnaire.

Results

The 6MWT was reduced in 45% of the population, while HGF, EFMS, QPT and HPT muscle strength were reduced in 15%, 12%, 27% and 18%, respectively. PImax was reduced in 43% of the population. The majority of the patients (81%) reported fatigue (FAS≥22). Patients with reduced peripheral muscle strength of the upper and/or lower extremities were more fatigued and demonstrated impaired lung functions, fat-free mass, PImax, 6MWT and quality of life. Fatigue was neither predicted by exercise capacity, nor by muscle strength.

Conclusion

Besides fatigue, exercise intolerance and muscle weakness are frequent problems in sarcoidosis. We therefore recommend physical tests in the multidisciplinary management of sarcoidosis patients, even in nonfatigued patients.

Introduction

Sarcoidosis is a multisystem disorder of unknown origin, which is characterised by noncaseating epithelioid cell granulomas. The clinical course of sarcoidosis is highly variable, and virtually every organ can be involved. The lungs are affected in >90% of sarcoidosis patients, but muscles are also frequently involved. Patients often present with nonspecific symptoms, such as general weakness, arthralgia, reduced exercise capacity and fatigue.[1]

Despite the fact that fatigue is a common disabling problem (with a reported prevalence of 30-90%) and a clear hallmark of sarcoidosis patients that affects quality of life (QoL), it still remains underestimated and poorly understood.[2] The aetiology of fatigue in sarcoidosis is still unclear, and is most probably multifactoral. Moreover, fatigue is difficult to objectify. Possible factors related to fatigue are general inflammation, sleeping disorders, depression and small-fibre neuropathy.[3] However, fatigue does not correlate with lung function test results.[2,4] Fatigue may be explained by peripheral muscle weakness and exercise intolerance, and both may be caused by multiple factors, such as sarcoidosis located in the skeletal muscle, decreased pulmonary function, negative vicious circle of physical deconditioning and cortico-steroid-induced myopathy.[5]

The influence of exercise capacity and muscle strength on fatigue has not been studied extensively in sarcoidosis, although reduced exercise capacity and general weakness are frequently reported symptoms. Patients with fatigue complaints are more likely to report problems of exercise intolerance compared with nonfatigued patients.[4] The 6-minute walk test (6MWT) is widely used to assess exercise capacity.[6] Previous research found that the 6-minute walking distance (6MWD) was reduced in sarcoidosis patients compared with healthy subjects.[7,8] Impairment of inspiratory muscle strength has been suggested as an important factor reducing 6MWD.[9] Alhamad[7] and Baughman *et al.*[8] found that 73% and 51% of their respective sarcoidosis populations had a 6MWD of <400 m.

In a study by Miller *et al.*[10], 67% of the sarcoidosis patients terminated their peak exercise test because of “leg complaints”, which was considered an indication of skeletal muscle weakness. Similarly, Spruit *et al.*[5] reported diminished peripheral muscle strength in patients with sarcoidosis suffering from fatigue, and reduced peripheral muscle strength correlated with exercise intolerance and fatigue. In line with this, Wirnsberger *et al.*[11] found reduced respiratory muscle strength and endurance time. However, the study populations were rather small or only included sarcoidosis patients with specific health complaints.

The primary aim of our study was to assess the prevalence of exercise intolerance, peripheral muscle weakness and fatigue in sarcoidosis patients. Additionally, the predictive value of exercise capacity, muscle strength and other clinical characteristics, including lung function test results, radiographic stages, prednisone usage and inflammatory markers, were studied.

Methods

Subjects

Between November 2008 and September 2009, symptomatic sarcoidosis patients referred to the interstitial lung disease care team of the Department of Respiratory Medicine at Maastricht University Medical Centre (MUMC; Maastricht, the Netherlands) were included in this study. Patients were diagnosed 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.[1] Clinical data were obtained from medical records. A healthy control group matched for age and sex (one control for two patients) was recruited from hospital employees and the surrounding community. These healthy subjects did not use any medication. The data were used as reference for exercise capacity and peripheral muscle strength. Written informed consent was obtained from all subjects. This case-control study was approved by the local Medical Ethics Committee of the MUMC.

Clinical data

At inclusion, forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured with a pneumotachograph (Masterlab; Jaeger, Würzburg, Germany). The diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single-breath method (Masterlab; Jaeger). Values were expressed as percentage of predicted value.[12]

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.[1]

Body composition was measured by single-frequency bioelectrical impedance analysis (RJL Systems Inc., Clinton Township, MI, USA) in the supine position on the right side. Fat-free mass (FFM) was calculated from height (m^2)/resistance and body weight using the Lukaski formula. In order to assess the degree of functional tissue depletion, FFM was adjusted for body size by calculating the FFM-index: FFM (kg)/height (m^2).[4]

The C-reactive protein (CRP) concentration was measured by a turbidimetric method on the SYNCHRON LX® (Beckman Coulter Inc., Fullerton, CA, USA). The normal value for CRP is <10 mg/l. The serum levels of soluble interleukin-2 receptor (sIL-2R) were analysed using commercially available Diaclone ELISA kits (Sanquin, Amsterdam, the Netherlands). Normal values are between 240-3,154 pg/ml.

Muscle strength and exercise capacity

The 6MWT was used to assess exercise capacity, and was performed according to the American Thoracic Society guideline.[13]

The Biodex System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY, USA) was used to measure isokinetic peak torques (in Nm) of the hamstrings and quadriceps of the dominant leg, with a velocity of 180° per second, as described previously.[14] The Biodex is a reliable and valid isokinetic dynamometer.[15]

The maximal isometric grip strength of the dominant hand (lbs) was measured with the Jamar dynamometer (Fabrication Enterprises Inc., Irvington, NY, USA), which is also a valid and reliable instrument.[16]

Maximal isometric strength of the elbow flexors was measured with the microFET (Biometrics, Almere, the Netherlands), an electronic, hand-held dynamometer, with the subject sitting in a chair. The ”break” method was used to measure the maximal peak force of the dominant arm in Newtons (N).[17] This hand-held dynamometer is a reliable measurement.[17]

Maximal inspiratory pressure (PImax) was assessed by measuring maximal respiratory mouth pressures using the method of Black and Hyatt.[18] Maximal inspiratory mouth pressure was measured at residual volume with a pressure transducer (model MP 45-30; Validyne Engineering Corp., Northridge, CA, USA).[4] Data from the study by Harik-Khan *et al.*[19] (n=267 healthy subjects) were used as reference values.

Questionnaires

Fatigue was measured with the 10-item Fatigue Assessment Scale (FAS), which indicates both physical and psychological fatigue. Each item has a five-point rating scale and FAS scores range from 10 to 50. FAS scores <22 indicate nonfatigued persons, scores of 22-34 indicate fatigued persons and scores of ≥35 indicate extremely fatigued persons.[20] The psychometric properties of the FAS are also good in sarcoidosis.[20]

The World Health Organization Quality of Life assessment instrument-BREF (WHOQOL-BREF) is a generic, cross-culturally developed comprehensive measure of QoL. It consists of 24 questions within four domains (physical health, psychological health, social relationships and environment) and two questions that compose the facet of overall QoL and general health. The psychometric properties of the WHOQOL-BREF appeared to be good.[21,22]

Statistical analysis

Demographic and clinical data are expressed as mean ± standard deviation (SD) and, if appropriate, in absolute numbers. To detect statistically significant differences between the patient and control groups, continuous data were analysed with independent-sample unpaired t-tests and nominal data were tested using Chi-squared tests.

Physical test results below the mean results of the control group minus 2SD (95% confidence interval) were assumed to indicate exercise intolerance or muscle strength impairment. The cut-off value for PImax, FVC, FEV_1 and DLCO was <80% of the predicted value.[12,19] Frequency distributions were used to determine the prevalence of exercise intolerance, reduced muscle strength and fatigue.

Associations between exercise capacity, muscle strength, fatigue and other clinical characteristics were calculated using Pearson's correlations. Differences in FAS scores in relation to sex, prednisone use and radiographic stages were explored by means of t-tests and one-way ANOVA. Variables with a significant association with fatigue were used for multiple regression analysis. A backward multiple regression analysis was used to develop a model to predict fatigue. A p-value <0.05 was considered to be statistically significant.

Differences between sarcoidosis patients with (group 4: combination of patients in group 2 (reduced muscle strength of arms) and group 3 (reduced muscle strength of legs)) and without (group 1: normal muscle strength of both arms and legs) peripheral muscle strength impairment with regard to physical and clinical characteristics were examined using independent-sample t-tests. Differences in nominal data were tested using Chi-squared tests. All analyses were performed using SPSS 15.0 for Windows (SPSS Inc.,Chicago, IL, USA).

Results

Patient and healthy control characteristics

During the study period, 145 sarcoidosis patients were referred to the outpatient clinic of the MUMC. Twenty one of the patients were not able to participate because they visited the hospital in a week when the maximum inclusion capacity of five subjects had already been reached. Thus, 124 sarcoidosis patients (mean age 46.6±10.2 yrs; 80 males and 44 females) were included. Clinical data are summarised in Table 3.1. FAS scores >21 points, indicating fatigue complaints, were reported in 101 (81%) patients, and 26% of these fatigued patients reported extreme fatigue (FAS ≥35). The mean body mass index (BMI) was 28.0±4.7 kg/m^2, which indicated some excess weight (BMI between 25-30 kg/m^2 indicates overweight). The pulmonary function tests showed that FEV_1 and DLCO, as a percentage of predicted values, were slightly reduced in this population. The clinical data of the healthy control group are also presented in Table 3.1. Sarcoidosis patients were significantly more fatigued compared with the healthy controls (p<0.001).

Table 3.1 Summary of demographic and clinical characteristics of the sarcoidosis patients and the healthy controls studied.

	Sarcoidosis patients	Healthy controls
Demographics		
Subjects	124	62
Females/males	44 / 80	22 / 40
Age (yrs)	46.6 ± 10.2	46.4 ± 9.9
Time since diagnosis (yrs)	6.1 ± 6.2	NA
BMI (kg/m^2)	28.0 ± 4.7[c]	24.7 ± 1.8
Nonsmoker/smoker/stopped <1 yr	106 / 11 / 7	56 / 6 / 0
Arthralgia (yes/no)	93 / 29[c]	0 / 62
Medication		
Prednisone use (yes/no)	48 / 76[c]	0 / 62
Prednisone dosage (mg)	13.2 ± 7.4	0
Methotrexate use (yes/no)	39 / 85[c]	0 / 62
Methotrexate dosage (mg)	10.8 ± 3.1	0
Lung function tests		
DLCO (% pred)	75.7 ± 17.6	NA
FVC (% pred)	98.3 ± 20.8	NA
FEV_1 (% pred)	84.2 ± 22.6	NA
Chest radiographic stages		
0/I/II/III/IV	28 / 18 / 32 / 14 / 32	NA
Inflammatory markers		
CRP[a]	8.6 ± 15.4	NA
sIL-2R[b]	3,282 ± 2,331	NA
Fatigue measure		
FAS score	28.3 ± 7.7[c]	15.6 ± 4.0
WHOQOL-BREF		
Facet overall QoL	5.9 ± 1.6[c]	8.7 ± 1.0
Physical health domain	12.3 ± 2.8[c]	17.9 ± 1.5

Data are expressed as absolute numbers (n) or mean ± standard deviation (SD). BMI: body mass index; DLCO: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; 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 assessment instrument-BREF; QoL: quality of life; NA: not applicable. [a] normal range <10 mg/l; [b] normal range 240-3,154 pg/ml; [c] $p<0.001$.

Exercise capacity

Sarcoidosis patients demonstrated a significantly shorter 6MWD compared with healthy controls (Table 3.2). The sarcoidosis population showed a mean reduction in exercise capacity of 20% (Table 3.2), >45% of the sarcoidosis patients demonstrated a reduction in exercise capacity.

Exercise capacity was reduced in 49% of the fatigued and in 30% of the nonfatigued patients (p=0.116). Patients with peripheral muscle strength impairment demonstrated a reduced 6MWD compared with patients without reduced peripheral muscle strength (p<0.001) (Table 3.3).

Table 3.2 Summary of the physical characteristics of the sarcoidosis patients and healthy controls studied.

	Total		Males		Females	
	Sarcoidosis	Healthy	Sarcoidosis	Healthy	Sarcoidosis	Healthy
Exercise capacity						
6MWD (m)	576 ± 124[c]	723 ± 80	607 ± 118[c]	747 ± 74	518 ± 115[c]	679 ± 73
6MWD (% pred)	79.5 ± 16.3		81.3 ± 15.8		76.3 ± 16.9	
Reduced 6MWD[a]	45.2	3.2	41.3	2.5	52.3	4.5
Muscle force						
HGF (lbs)	94.4 ± 33.3	97.9 ± 27.8	110.7 ± 25.9	115.5 ± 15.1	64.1 ± 22.4	65.9 ± 12.5
HGF (% pred)	96.3 ± 27.0		95.8 ± 22.5		97.1 ± 34.0	
Reduced HGF[a]	15.4	3.2	16.3	2.5	14.0	4.5
EFMS (N)	219.5 ± 72.2[b]	242.8 ± 72.4	255.8 ± 58.8[b]	287.0 ± 47.9	150.4 ± 35.8	162.6 ± 22.9
EFMS (% pred)	90.3 ± 21.0		89.1 ± 20.5		92.5 ± 22.0	
Reduced EFMS[a]	12.3	3.2	10.0	2.5	16.7	4.5
QPT (Nm)	80.9 ± 36.1[c]	101.3 ± 30.6	95.6 ± 34.0[c]	118.4 ± 23.0	53.9 ± 21.1[c]	70.2 ± 13.3
QPT (% pred)	79.3 ± 29.1		80.8 ± 28.7		76.7 ± 30.0	
Reduced QPT[a]	27.0	6.5	22.8	5.0	34.9	9.1
HPT (Nm)	61.5 ± 26.6[c]	75.3 ± 23.0	71.4 ± 26.0[c]	86.3 ± 18.7	43.2 ± 16.2[b]	55.3 ± 15.3
HPT (% pred)	81.3 ± 29.7		82.9 ± 30.1		78.3 ± 29.1	
Reduced HPT[a]	18.0	0	20.3	0	14.0	0
PImax (cmH_2O)	-82.5 ± 29.5	NA	-90.7 ± 30.7	NA	-67.7 ± 20.1	NA
PImax (% pred)	82.5 ± 28.5		80.2 ± 25.9		86.6 ± 32.8	
Reduced PImax[a]	43.1		44.3		41.0	

Data are expressed as mean ± standard deviation (SD) or percentages (%). 6MWD: 6-minute walking distance; % pred: % predicted; HGF: handgrip force; EFMS: elbow flexor muscle strength; QPT: quadriceps peak torque; HPT: hamstrings peak torque; PImax: maximal inspiratory pressure; NA: not applicable. [a]: percentage of subjects below the mean results minus 2SD of the control group; [b] $p<0.05$; [c] $p<0.001$.

Muscle strength

Peripheral muscle strength, i.e. elbow flexor muscle strength, and quadriceps and hamstrings peak torque, was significantly lower in the sarcoidosis patients compared to the control subjects (Table 3.2). No differences were found in handgrip force between both groups.

Handgrip force, elbow flexor muscle strength, quadriceps peak torque, hamstrings peak torque and PImax were reduced in 15%, 12%, 27%, 18% and 43% of the population, respectively (Table 3.2).

A substantial proportion of the fatigued and nonfatigued patients showed a reduction in handgrip force (18% and 4%, respectively; p=0.102), elbow flexor muscle strength (12% and 13%, respectively; p=0.903), quadriceps peak torque (27% and 26%, respectively; p=0.908), hamstrings peak torque (19% and 13%, respectively; p=0.490) and PImax (47% and 26%, respectively; p=0.083).

Patients with reduced peripheral muscle strength of the upper limbs (group 2: n=24), lower limbs (group 3: n=37) or both (group 4: n=45) differed from patients without peripheral muscle strength impairment (group 1: n=79) with regard to fatigue (Table 3.3). The overall QoL and the QoL domain physical health, as well as the lung function test results, FFM, PImax and 6MWD, were found to be impaired in the

subgroup with reduced peripheral muscle strength compared to patients without muscle strength impairment (Table 3.3). Neither peripheral muscle strength nor PImax was found to be related to prednisone dose.

Table 3.3 Summary of clinical characteristics of the sarcoidosis patients studied stratified by upper- and lower-extremity muscle strength.

	Group 1: normal muscle strength	Group 2: reduced HGF and/or EFMS	Group 3: reduced QPT and/or HPT	Group 4: reduced muscle strength of arms and/or legs	p-value[a]
Demographics					
Subjects	79	24	37	45	
Prednisone use (yes/no)	29 / 50	11 / 13	16 / 21	19 / 26	0.544
Prednisone dosage (mg)	14.2 ± 7.8	12.0 ± 5.6	12.5 ± 6.9	11.7 ± 6.7	0.267
Methotrexate use (yes/no)	25 / 54	7 / 17	12 / 25	14 / 31	0.951
Methotrexate dosage (mg)	11.6 ± 2.2	10.0 ± 5.0	9.0 ± 4.1	9.3 ± 4.1	0.065
Lung function tests					
DLCO (% pred)	79.6 ± 17.2	68.8 ± 16.6	66.9 ± 15.9	68.7 ± 16.3	0.001
FVC (% pred)	101.5 ± 21.6	89.0 ± 17.4	91.7 ± 18.8	92.7 ± 18.3	0.023
FEV_1 (% pred)	87.4 ± 21.7	78.0 ± 23.6	76.2 ± 23.6	78.6 ± 23.2	0.037
Inspiratory muscle strength					
PImax (% pred)	88.3 ± 25.7	67.4 ± 32.0	78.6 ± 30.7	72.1 ± 30.7	0.004
Exercise capacity					
6MWD (% pred)[b]	86.7 ± 12.5	63.3 ± 16.3	68.3 ± 14.2	67.1 ± 14.6	<0.001
Chest radiographic stage	2.1 ± 1.4	1.9 ± 1.7	2.1 ± 1.7	2.0 ± 1.7	0.864
Inflammatory markers					
CRP[c]	7.2 ± 14.1	8.6 ± 12.7	11.1 ± 17.4	11.0 ± 17.3	0.193
sIL-2R[d]	3,452 ± 2,472	2,897 ± 2,028	3,159 ± 2,121	2,958 ± 2,028	0.281
Body composition					
BMI (kg/m^2)	28.2 ± 4.4	28.3 ± 4.9	27.7 ± 5.2	28.0 ± 5.2	0.783
FFM (kg)	57.1 ± 10.3	54.1 ± 10.7	50.5 ± 9.8	52.2 ± 10.0	0.016
FFM index (kg/m^2)	18.2 ± 2.4	17.9 ± 2.7	17.0 ± 2.9	17.4 ± 2.8	0.095
Fatigue					
FAS score	27.1 ± 7.4	32.0 ± 8.2	30.3 ± 8.3	30.4 ± 7.8	0.023
WHOQOL-BREF					
Facet overall QoL	6.2 ± 1.4	5.2 ± 1.6	5.2 ± 1.8	5.4 ± 1.7	0.004
Physical health domain	13.1 ± 2.7	10.7 ± 2.4	11.0 ± 2.8	11.0 ± 2.7	<0.001

Data are expressed as absolute numbers (n) or mean ± standard deviation (SD), unless otherwise stated. HGF: handgrip force; EFMS: elbow flexor muscle strength; QPT: quadriceps peak torque; HPT: hamstrings peak torque; DLCO: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; PImax: maximal inspiratory pressure; 6MWD: 6-minute walking distance; CRP: C-reactive protein; sIL-2R: soluble interleukin-2 receptor; BMI: body mass index; FFM: fat-free mass; FAS: Fatigue Assessment Scale; WHOQOL-BREF: World Health Organization Quality of Life assessment instrument-BREF; QoL: quality of life. [a] group 1 compared to group 4; [b] % of mean results of the control group; [c] normal range <10 mg/l; [d] normal range 240-3,154 pg/ml.

Relationship between fatigue and clinical parameters

Fatigue showed weak correlations with exercise capacity and muscle strength parameters in male patients but not in female patients (Table 3.4). In the female

patients only, BMI (r=0.329, p=0.029) showed a significant positive correlation with fatigue. In both sexes, fatigue was unrelated to demographic characteristics (age, FFM and time since diagnosis), lung function test results (FVC% pred and FEV_1% pred) and levels of inflammatory markers (CRP and sIL-2R). FAS scores did not differ regarding sex (t=0.426, p=0.671), oral prednisone use (t=-1.011, p=0.314) or radiographic stages (F-score 0.507 (df regression 4, df residual 119), p=0.730).

In multiple regression analyses, only hamstrings peak torque was a significant predictor of fatigue in male patients, predicting 14.3% of the FAS score (p=0.001; ß=0.114).

Table 3.4 Correlations between Fatigue Assessment Scale (FAS) scores and the absolute values of the physical characteristics of the 80 male and 44 female sarcoidosis patients studied.

FAS scores	6MWD	HGF	EFMS	QPT	HPT	PImax
Males	-0.25 (0.024)	-0.25 (0.023)	-0.29 (0.010)	-0.17 (0.131)	-0.36 (0.001)	0.24 (0.047)
Females	-0.12 (0.425)	-0.21 (0.171)	-0.30 (0.055)	-0.04 (0.824)	-0.043 (0.783)	0.051 (0.756)

Data are expressed as Pearson correlation (p-value). 6MWD: 6-minute walking distance; HGF: handgrip force; EFMS: elbow flexor muscle strength; QPT: quadriceps peak torque; HPT: hamstrings peak torque; PImax: maximal inspiratory pressure.

Discussion

The main finding of this study is that a substantial number of patients with symptomatic sarcoidosis display exercise intolerance (45%), as well as muscle weakness (prevalence rates of 12-27%) and fatigue (81%). Exercise intolerance and reduced muscle strength occurred in both fatigued and nonfatigued sarcoidosis patients. Patients with impaired peripheral muscle strength were more fatigued and demonstrated impaired lung function test results, FFM, PImax, 6MWD and QoL compared with patients without reduced peripheral muscle strength. Fatigue was neither predicted by exercise capacity, nor by muscle strength. Hamstrings peak torque accounted for only 14% of the variance of the FAS score in male patients.

Exercise intolerance was present in a substantial number of the studied sarcoidosis patients, especially in those with reduced peripheral muscle strength. In line with this, Kabitz *et al.*[9] also found reduced 6MWD in male sarcoidosis patients compared to healthy males. Similarly, Spruit *et al.*[5] found reduced 6MWD in sarcoidosis patients complaining of fatigue compared with healthy subjects, and Alhamad[7] and Baughman *et al.*[8] reported even lower 6MWD. The differences in 6MWD between studies were not explained by clinical characteristics. A factor that might explain differences in 6MWD in different sarcoidosis populations may be ethnicity. The study by Alhamad *et al*.[7] involved Saudi Arabian sarcoidosis patients. Al-Nozha *et al.*[23] reported a high prevalence of physical inactivity (96.1%) in general among Saudi Arabian adults.

In the present study, muscle weakness was found in a substantial proportion of our study population, even in the absence of fatigue. Measurement of muscle strength of either the upper or lower body provided complementary information even when patients were not fatigued. The mean handgrip force and PImax were comparable with the results reported by Spruit *et al.*[5], who found peripheral and PImax impairment in sarcoidosis patients complaining of fatigue. However, the quadriceps peak torques found in the study by Spruit *et al.*[5] cannot be compared to those in the present study, as they measured isometric quadriceps forces, while the present study measured isokinetic quadriceps forces. Although Wirnsberger *et al.*[11] did not find peripheral muscle weakness in sarcoidosis patients, they did find a tendency towards reduced peripheral muscle strength. The sample size of their study population was rather small. Drent *et al.*[4] demonstrated that fatigued patients were more likely to suffer from exercise intolerance than nonfatigued patients. Nevertheless, our study found fatigue to be only weakly related to both exercise capacity and muscle strength. Both fatigued and nonfatigued sarcoidosis patients have to cope with the complaints of reduced muscle strength and exercise intolerance. Drent *et al.*[4] also found reduced FFM in their studied fatigued patients. In the present study, the FFM was found to be decreased in patients with reduced peripheral muscle strength. Reduction of FFM is an expression of muscle wasting.[24] Although not directly measured in the present study, it is assumed that muscle wasting, i.e. loss of muscle bulk, might be a determinant of strength as in other chronic disorders.

Fatigue is a prominent problem in sarcoidosis and is frequently related to an impaired QoL. Previous studies have shown a wide range of fatigue rates (30-90%) in sarcoidosis patients.[2] Nevertheless, the majority of studies show fatigue prevalence rates between 70% and 90%.[2] The prevalence of fatigue in the present study was 81%. It is important to consider that most of the patients we studied were suffering from severe sarcoidosis, as this was the main reason why they were referred to a tertiary referral centre in the Netherlands.

Despite the complex and multifaceted aetiology of fatigue, several investigators have attempted to elucidate the potential causes of fatigue in sarcoidosis. Most of these studies evaluated clinical parameters, with only a few studies postulating psychological factors, such as underlying mechanisms of fatigue.[25] De Vries *et al.*[2] found no relationship between fatigue in sarcoidosis patients and a number of clinical variables, including pulmonary function, metabolic variables, laboratory parameters of inflammation and T-cell activation and granuloma formation. The present study investigated a multifactorial explanation of fatigue. In line with De Vries *et al.*[2], we did not find a relationship between fatigue and parameters commonly used to assess fatigue in sarcoidosis (demographic patient characteristics, lung function tests, radiographic stages and corticosteroid use). The aetiology of fatigue may involve general inflammation, and Drent *et al.*[4] found that an acute phase response (CRP levels) was associated with fatigue complaints in sarcoidosis. In the present study, however,

CRP levels were unrelated to fatigue, which is in line with De Vries *et al.*[2] In the present study, fatigue showed only a weak relationship with peripheral muscle strength.

Reduced exercise capacity, muscle weakness, loss of FFM and fatigue have been described in association with various chronic inflammatory diseases, such as Crohn's disease and rheumatoid arthritis.[26,27] Sarcoidosis patients also often present with exercise intolerance, general weakness and fatigue. The number of studies on this topic among sarcoidosis patients is limited, and most studies only included small study populations or sarcoidosis patients with specific health complaints.[5,11] Nevertheless, the primary causes of these physical disabilities and their interrelations remain unclear for sarcoidosis too.

Study limitations

The present study was a cross-sectional study and, therefore, no conclusions could be drawn with regard to causality. This study only included refractory sarcoidosis patients suffering from severe physical complaints who were referred to a tertiary hospital, which may have caused selection bias. This selection might have resulted in an overestimation of the prevalence of reduced exercise capacity, muscle weakness and fatigue.

Both the 6MWT and the muscle strength tests are volitional tests. The results of these tests partially depend on the patient's motivation and cooperation during the test. Nonvolitional testing would probably yield more valid results. However, these tests used are generally accepted in clinical studies[5,6,28] and, to our knowledge, sarcoidosis patients are very cooperative and motivated to participate in research projects.

In the literature, normative values for the 6MWT[29], handgrip force[16], elbow flexor muscle strength[30], and quadriceps and hamstrings peak torque[14] do exist. Our control group data are comparable with the normative values.

In conclusion, the present study showed exercise intolerance, muscle weakness and fatigue to be frequent problems in sarcoidosis. Although the majority of the patients in our study suffered from fatigue, exercise intolerance and muscle weakness occurred in both fatigued and nonfatigued patients. Patients with peripheral muscle strength impairment of the upper or lower body or both were more fatigued and demonstrated impaired lung function test results, FFM, PImax, 6MWD and QoL. Fatigue was not predicted by clinical parameters. More research is needed to standardise the assessment of exercise intolerance, muscle strength and fatigue in sarcoidosis. Research as to whether a multidisciplinary rehabilitation programme is of clinical benefit in the management of sarcoidosis patients is extremely necessary.

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