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Exercise capacity, muscle strength and fatigue in sarcoidosis

R.G.J. Marcellis[1,2], A.F. Lenssen[1], M.D.P. Elfferich[1,2], J. De Vries[2,3], S. Kassim[1], K. Foerster[1], and M. Drent[2,4]

[1]Department of Physical Therapy, [2]ild care center, Maastricht University Medical Centre (MUMC), [3]Department of Medical Psychology, St. Elisabeth Hospital Tilburg & CoRPS, Department of Medical Psychology, Tilburg University, [4]Department of Respiratory Medicine, MUMC, The Netherlands

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Correspondence and requests for reprints should be addressed to:

Prof. dr. M. Drent, Department of Respiratory Medicine, ild care center

Maastricht University Medical Centre (MUMC)

PO BOX 5800, 6202 AZ Maastricht, The Netherlands

Phone: +31 43 3876497

Fax: +31 43 3874718

E-mail: m.drent@mumc.nl

Website: www.pul.unimaas.nl; www.ildcare.eu

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ABSTRACT: The aim of the 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).

Sarcoidosis patients referred to the Maastricht University Medical Centre were included (124 patients; mean age: 46.6±10.2 years; 80 men). Patients performed a six-minute walk test (6MWT), handgrip (HGms), elbow flexor (EFms), quadriceps (Qms), hamstrings (Hms) and inspiratory muscle strength tests (*P*i,max) and completed the Fatigue Assessment Scale (FAS).

The 6MWT was reduced in 45% of the population, while HGms in 15%, EFms in 12%, Qms in 27%, Hms in 18% and *P*i,max 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, FFM, *P*i,max, 6MWT and quality of life. Fatigue was neither predicted by exercise capacity, nor by muscle strength.

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 non-fatigued patients.

INTRODUCTION

Sarcoidosis is a multisystem disorder of unknown origin, which is characterized 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 more than 90% of sarcoidosis patients, but muscles are also frequently involved. Patients often present with non-specific 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 affecting quality of life (QOL), it still remains underestimated and poorly understood.[2] The aetiology of fatigue in sarcoidosis is still unclear, and is most likely 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 did 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 corticosteroid-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 mentioned symptoms. Patients with fatigue complaints are more likely to report problems of exercise intolerance compared to non-fatigued patients.[4] The six-minute walk test (6MWT) is widely used to assess exercise capacity.[6] Previous research found that the six-minute walking distance (6MWD) was reduced in sarcoidosis patients compared to healthy subjects.[7, 8] Impairment of inspiratory muscle strength has been suggested as an

important factor reducing 6MWD.[9] Alhamad et al.[7] and Baughman et al.[8] found that 73% and 51% of their respective sarcoidosis populations had a 6MWD of less than 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 the present 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 for fatigue were studied.

METHODS

Subjects

Between November 2008 and September 2009, symptomatic sarcoidosis patients referred to the ild (interstitial lung disease) care team of the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC) 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 WASOG guidelines.[1] Clinical data were obtained from the 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, the 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 for carbon monoxide (DLCO) was measured by the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Values were expressed as a percentage of predicted value.[12]

Chest radiographs were graded according to the radiographic staging proposed by DeRemee (0 to III), adding stage IV, with 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, Detroit, USA) in the supine position on the right side. Fat-free mass (FFM) was

calculated from height^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^2 (m^2)).[4]

The C-reactive protein (CRP) concentration was measured by a turbidimetric method on the SYNCHRON LX® (Beckman Coulter Inc., Fullerton, CA). The normal value for CRP is <10mg.L^{-1}. The serum levels of soluble IL-2 Receptor (sIL-2R) were analysed in commercially available Diaclone ELISA kits (Sanquin, Amsterdam, The Netherlands). Normal values are between 240-3154 pg.mL^{-1}.

Muscle strength and exercise capacity

The Six-Minute Walk Test (6MWT) was used to assess exercise capacity, and was performed according to the American Thoracic Society guideline.[13]

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

The maximal isometric grip strength of the dominant hand (in pounds) was measured with the Jamar dynamometer, which is also a valid and reliable instrument.[16]

Maximal isometric strength of the elbow flexors was measured with the microFET, 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 Newton (N).[17] This hand-held dynamometer is a reliable measurement.[17]

Inspiratory muscle strength (*P*i,max) was assessed by measuring maximal respiratory mouth pressures using the method of black and Hyatt. 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. (n= 267 healthy subjects) were used as reference values.[18]

Questionnaires

Fatigue was measured with the 10-item Fatigue Assessment Scale (FAS), which indicates both physical and psychological fatigue. Each item has a 5-point rating scale and FAS scores range from 10 to 50. FAS scores below 22 indicate non-fatigued persons, scores of 22-34 indicate fatigued persons and scores of 35 or more indicate extremely fatigued persons.[19] The psychometric properties of the FAS are good, also in sarcoidosis.[19]

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, Environment) and two questions that compose the facet Overall QOL and General health. The psychometric properties of the WHOQOL-Bref appeared to be good.[20, 21]

Statistical analysis

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

Physical test results below the mean results of the control group minus two times SD (95%CI) were assumed to indicate exercise intolerance or muscle strength impairment. The cut-off value for *P*i,max, FVC, FEV_1 and DLCO was <80% of the predicted value.[12, 18] 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 a 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. P-values <0.05 were considered 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-square tests.

All analyses were performed using SPSS 15.0 for Windows.

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 had already been reached. Thus, 124 sarcoidosis patients (mean age: 46.6±10.2 years; 80 men, 44 women) were included. Clinical data are summarized in table 1. FAS scores >21 points, indicating fatigue complaints, were reported in 101 patients (81%), 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 overweight (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 presented in table 1. Sarcoidosis patients were significantly more fatigued compared with the healthy controls ($p<0.001$).

Exercise capacity

Sarcoidosis patients demonstrated a significantly shorter 6MWD compared to healthy controls (table 2). The sarcoidosis population showed a mean reduction in exercise capacity of 20% (table 2). More than 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 non-fatigued 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).

Muscle strength

Peripheral muscle strength, i.e. elbow flexor muscle strength, quadriceps and hamstrings peak torque, was significantly lower in the sarcoidosis patients compared to the control subjects (table 2). No differences were found in handgrip force between both groups.

The handgrip force was reduced in 15%, elbow flexor muscle strength in 12%, quadriceps peak torque in 27%, hamstrings peak torque in 18% and *P*i,max in 43% of the population (table 2).

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

Patients with reduced peripheral muscle strength of the upper (group 2; n=24), lower (group 3; n=37) or both extremities (group 4; n=45) differed from patients without peripheral muscle strength impairment (group1; n=79) with regard to fatigue (table 3). The overall QOL and the QOL domain physical health as well as the lung function test results, FFM, *P*i,max and 6MWD were found to be impaired in the subgroup with reduced peripheral muscle strength compared with patients without muscle strength impairment (table 3). Neither peripheral muscle strength nor *P*i,max was found to be related to the used prednisone dose.

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 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% and FEV_1%) and levels of inflammatory markers (CRP and sIL2R). FAS

scores did not differ regarding gender (t= 0.426, p= 0.671), oral prednisone use (t= -1.011, p= 0.314) or radiographic stages (F(4, 119) = 0.507, p= 0.730).

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

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 between 12-27%) and fatigue (81%). Exercise intolerance and reduced muscle strength occurred in both fatigued and non-fatigued sarcoidosis patients. Patients with impaired peripheral muscle strength were more fatigued and demonstrated impaired lung function test results, FFM, *P*i,max, 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 explained just 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 6MWDs in male sarcoidosis patients compared to healthy men. Similarly, Spruit et al.[5] found reduced 6MWDs in sarcoidosis patients complaining of fatigue compared with healthy subjects, and Alhamad et al.[7] and Baughman et al.[8] reported even lower 6MWDs. The differences in 6MWD between authors were not explained by clinical characteristics. A factor that might explain differences in 6MWDs in different sarcoidosis populations may be ethnicity. The study by Alhamad et al.[7] involved Saudi-Arabian sarcoidosis patients. Al-Nozha et al.[22] reported a high prevalence of physical inactivity (96.1%) in general among Saudi adults.

In the present study, muscle weakness was found in a substantial part of our study population even in the absence of fatigue. Measurement of either muscle strength of the upper and lower extremities provided complementary information even when patients are not fatigued. The mean handgrip force and *P*i,max were comparable with the results reported by Spruit et al.[5] who found peripheral and *P*i,max impairment in sarcoidosis patients complaining of fatigue. However, the quadriceps peak torques found in the study by Spruit et

al. 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 found 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 non-fatigued patients. Nevertheless, the present study found fatigue to be only weakly related to both exercise capacity and muscle strength. Both fatigued and non-fatigued sarcoidosis patients have to cope with 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.[23] 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 like in other chronic disorders.

Fatigue is a prominent problem in sarcoidosis and is frequently related to an impaired QOL. Previous studies showed 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 as underlying mechanisms of fatigue.[24] 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], the present study 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 (C-reactive protein (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 only showed a weak relation with peripheral muscle strength.

Reduced exercise capacity, muscle weakness, loss of fat free mass and fatigue have been described in association with various chronic inflammatory diseases, such as Crohn's disease and rheumatoid arthritis.[25, 26] 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 and 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 6-minute walk test and the muscle strength tests are volitional tests. The results of these tests partially depend on the patient's motivation and co-operation during the test. Probably non-volitional testing would yield more valid results. However, the tests used are generally accepted in clinical studies [5, 6, 27] and to our experience, sarcoidosis patients are very cooperative and motivated to participate in research projects.

In the literature, normative values for the 6MWT [28], handgrip force [16], elbow flexor muscle strength [29], 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 non-fatigued patients. Patients with peripheral muscle strength impairment of the upper or lower extremities or both were more fatigued and demonstrated impaired lung function test results, FFM, *P*i,max, 6MWD, and QOL. Fatigue was not predicted by clinical parameters. More research is needed to standardize the assessment of exercise intolerance, muscle strength and fatigue in sarcoidosis. Research whether a multidisciplinary rehabilitation programme is of clinical benefit in the management of sarcoidosis patients is really necessary.

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TABLE 1 Summary of demographic and clinical characteristics of the sarcoidosis population and the healthy controls studied

	Total group	**Healthy controls**
Demographic		
Number of patients (female/male)	124 (44/80)	62 (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*	24.7 ± 1.8
Nonsmoker/smoker/stopped < 1 year, n	106/11/7	56/6/0
Arthralgia yes/no, n	93 /29*	0/62
Medication		
Prednisone use yes/no, n	48/76*	0/62
Prednisone dosage, mg	13.2 ± 7.4	0
Methotrexate use yes/no, n	39/85*	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, n	28/18/32/14/32	NA
Inflammatory markers		
CRP, < 10 $mg.L^{-1}$	8.6 ± 15.4	NA
sIL-2R, 240-3154 $pg.mL^{-1}$	3282 ± 2331	NA

Fatigue measure		
FAS score	28.3 ± 7.7*	15.6 ± 4.0
WHOQOL-Bref		
Facet Overall QOL	5.9 ± 1.6*	8.7 ± 1.0
Domain Physical Health	12.3 ± 2.8*	17.9 ± 1.5

Data are expressed as mean ± SD, or absolute numbers if appropriate.

BMI: body mass index; DLCO: carbon monoxide diffusing capacity; % pred: % of predicted values; 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.

NA: not applicable. *$p<0.001$.

TABLE 2 Summary of the physical characteristics of the sarcoidosis population and healthy controls studied

	Total sarcoidosis group	**Healthy controls**	**Sarcoidosis men**	**Healthy control men**	**Sarcoidosis women**	**Healthy control women**
Exercise capacity						
6MWD, m	576 ± 124*	723 ± 80	607 ± 118*	747 ± 74	518 ± 115*	679 ± 73
6MWD, % pred	79.5 ± 16.3		81.3 ± 15.8		76.3 ± 16.9	
% reduced 6MWD	45.2	3.2	41.3	2.5	52.3	4.5
Muscle force						
Handgrip force (HGF), pounds	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	15.4	3.2	16.3	2.5	14.0	4.5
Elbow flexor muscle strength (EFMS), N	219.5 ± 72.2**	242.8 ± 72.4	255.8 ± 58.8**	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	12.3	3.2	10.0	2.5	16.7	4.5

Quadriceps peak torque (QPT), Nm	80.9 ± 36.1*	101.3 ± 30.6	95.6 ± 34.0*	118.4 ± 23.0	53.9 ± 21.1*	70.2 ± 13.3
QPT, % pred	79.3 ± 29.1		80.8 ± 28.7		76.7 ± 30.0	
% reduced QPT	27.0	6.5	22.8	5.0	34.9	9.1
Hamstrings peak torque (HPT), Nm	61.5 ± 26.6*	75.3 ± 23.0	71.4 ± 26.0*	86.3 ± 18.7	43.2 ± 16.2**	55.3 ± 15.3
HPT, % pred	81.3 ± 29.7		82.9 ± 30.1		78.3 ± 29.1	
% reduced HPT	18.0	0	20.3	0	14.0	0
*P*i,max, cmH_2O	-82.5 ± 29.5	NA	-90.7 ± 30.7	NA	-67.7 ± 20.1	NA
*P*i,max, % pred	82.5 ± 28.5		80.2 ± 25.9		86.6 ± 32.8	
% reduced *P*i,max	43.1		44.3		41.0	

Data are expressed as mean ± SD, or percentages if appropriate.

6MWD: six-minute walking distance; % pred: % of mean results of the control group; % reduced: number of subjects below the mean results minus 2SD of the control group; *P*i,max: maximal inspiratory pressure. * $p< 0.001$ **$p<0.05$

TABLE 3 Summary of clinical characteristics of the sarcoidosis population studied, stratified by upper and lower extremity muscle strength

	Group 1 Normal muscle strength	Group 2 Reduced handgrip force and/or elbow flexor muscle strength	Group 3 Reduced quadriceps and/or hamstrings peak torque	Group 4 Reduced muscle strength of arms and/or legs	p-value Group 1 compared to Group 4
Demographic					
Number of patients, n	79	24	37	45	
Prednison use yes/no, n	29/50	11/13	16/21	19/26	0.544
Prednison dosage, mg	14.2 ± 7.8	12.0 ± 5.6	12.5 ± 6.9	11.7 ± 6.7	0.267
MTX use yes/no, n	25/54	7/17	12/25	14/31	0.951
MTX 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					
Pi,max, % pred	88.3 ± 25.7	67.4 ± 32.0	78.6 ± 30.7	72.1 ± 30.7	0.004
Exercise capacity					
6MWD, % pred*	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, < 10 $mg.L^{-1}$	7.2 ± 14.1	8.6 ± 12.7	11.1 ± 17.4	11.0 ± 17.3	0.193

sIL-2R, 240-3154 $pg.mL^{-1}$	3452 ± 2472	2897 ± 2028	3159 ± 2121	2958 ± 2028	0.281
Body composition					
Body mass index, $kg.m^{-2}$	28.2 ± 4.4	28.3 ± 4.9	27.7 ± 5.2	28.0 ± 5.2	0.783
Fat free mass (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
Domain Physical health	13.1 ± 2.7	10.7 ± 2.4	11.0 ± 2.8	11.0 ± 2.7	<0.001

Data are expressed as mean ± SD, or absolute numbers.

DLCO: carbon monoxide diffusing capacity; % pred: % of predicted values; % pred*: % of mean results of the control group; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; 6MWD: six-minute walking distance; *P*i,max: maximal inspiratory pressure; 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.

TABLE 4 Correlations between FAS scores and the absolute values of the physical characteristics of both male (N=80) and female (N=44) sarcoidosis patients studied

FAS scores	6MWD	HGF	EFMS	QPT	HPT	*P*i,max
Men	-0.25 (0.024)	-0.25 (0.023)	-0.29 (0.010)	-0.17 (0.131)	-0.36 (0.001)	0.24 (0.047)
Women	-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)

FAS: Fatigue Assessment Scale; 6MWD: six-minute walking distance; HGF: handgrip force; EFMS: elbow flexor muscle strength; QPT: quadriceps peak torque; HPT: hamstrings peak torque; *P*i,max: maximal inspiratory pressure.