Physical Activity and Fatigue in Patients with Sarcoidosis

Thomas Bahmer^{a, d} Henrik Watz^{b, d} Maria Develaska^c Benjamin Waschki^{a, d}
Klaus F. Rabe^{a, d} Helgo Magnussen^{b, d} Detlef Kirsten^{a, d} Anne-Marie Kirsten^{b, d}

^aPneumology, LungenClinic Grosshansdorf, Grosshansdorf, Germany; ^bPulmonary Research Institute, LungenClinic Grosshansdorf, Grosshansdorf, Germany; ^cLungenpraxis im Alstertal, Hamburg, Germany; ^dAirway Research Center North (ARC), German Center for Lung Research (DZL), Grosshansdorf, Germany

Keywords

Physical activity · Sarcoidosis · Rare lung diseases · Fatigue · Quality of life · 6-min walk test

Abstract

Background: Little is known about physical activity in daily life among patients with sarcoidosis. Fatigue is a frequent and disabling symptom that might negatively affect physical activity levels. **Methods:** In patients with sarcoidosis, we measured physical activity (steps per day) by accelerometry (SenseWear Armband) for 1 week. We assessed lung function (DLCO, FVC), exercise capacity (6-min walking distance [6MWD]), health-related quality of life (St George's Respiratory Questionnaire [SGRQ]), generic quality of life (12-Item Short-Form Health Survey [SF-12]), and fatigue (Multidimensional Fatigue Inventory [MFI-20]). **Results:** We investigated 57 patients with sarcoidosis (mean age 50 years, 56% male, mean DLCO 73% predicted, mean FVC 91% predicted, mean 6MWD 525 m, mean steps per day 7,490), of whom $n = 14$ (25%) had severe fatigue. The MFI-20 subscales "reduced activity" and "physical fatigue" were weakly associated with steps per day on a bivariate level (Spearman $\rho = -0.274$ and $\rho = -0.277$, respectively; $p < 0.05$), while the other subscales and the total score were not. 6MWD, SGRQ score, and SF-12

(physical health) score showed stronger associations with steps per day in bivariate analyses (Pearson $r = 0.499$, $r = -0.386$, and $r = 0.467$, respectively; $p < 0.01$), and were independent predictors of steps per day in multivariate linear regression analyses adjusting for confounders ($p < 0.05$). In ROC curve analyses, 6MWD, SGRQ score, and SF-12 (physical health) score properly identified sedentary patients (steps per day $< 5,000$; AUROC 0.90, 0.81, and 0.80, respectively; $p < 0.01$). Fatigue was less predictive (MFI-20 subscale "general fatigue," AUROC 0.70; $p = 0.03$). **Conclusion:** While exercise capacity and quality of life measurements were robust predictors of physical activity in patients with sarcoidosis, associations of objectively measured physical activity with fatigue were surprisingly weak. In sarcoidosis, fatigue might not preclude affected patients from being physically active, although this symptom is subjectively perceived as highly disabling.

© 2017 The Author(s)
Published by S. Karger AG, Basel

Introduction

Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic systems of the body [1]. Disease severity at the time of diagnosis, the number of affected organs, and the future disease course

vary widely between patients [2]. The clinical impact of sarcoidosis does not only result from specific organ manifestations and related functional consequences, but also from rather nonspecific symptoms such as fatigue, which is perceived as highly disabling by affected patients. The underlying causes of this complex symptom remain elusive, and functional measures such as exercise capacity and lung function show rather loose associations with fatigue in these patients [3–7].

Interestingly, fatigue has recently been linked to objective measures of physical activity in daily life in other chronic lung diseases such as idiopathic pulmonary fibrosis [8], lymphangioleiomyomatosis [9], and chronic obstructive pulmonary disease [10], suggesting that it might also affect physical activity in patients with sarcoidosis. However, studies on objectively measured physical activity in patients with sarcoidosis are rather limited, and the results are conflicting [11, 12]. While one study found physical activity in patients with sarcoidosis and fatigue to be reduced compared to predicted reference values [12], Saligan [11] was not able to show meaningful differences between obese patients with sarcoidosis and sedentary controls. In chronic lung diseases, established clinical parameters such as exercise capacity and lung function, or patient-reported outcomes such as health-related quality of life and generic quality of life, generally show moderate associations with levels of objectively measured physical activity [8–10]. However, to the best of our knowledge, those relationships have not yet been investigated in patients with sarcoidosis.

In our study, we aimed to evaluate the relationships between daily physical activity and established clinical assessment parameters in patients with sarcoidosis. Furthermore, we wanted to explore whether fatigue and its different domains are associated with physical activity impairments in patients with sarcoidosis.

Methods

Study Population

We prospectively recruited patients with a proven diagnosis of sarcoidosis that were in follow-up care at the outpatient department for sarcoidosis and interstitial lung diseases at LungenClinic Grosshansdorf. We documented organ involvement (i.e., pulmonary and/or extrapulmonary), chest radiography stages (i.e., 0–IV) for pulmonary involvement, and current treatment.

The study was approved by the local ethics committee of Schleswig-Holstein (ethics approval [AZ 038/12 II]; German Clinical Trials Register No. DRKS00006170). Recruitment took place between August 2012 and March 2014. All participants provided written informed consent prior to inclusion.

Lung Function and Exercise Capacity

Measurements of spirometry (forced vital capacity [FVC], forced expiratory volume at 1 s [FEV₁]) and diffusing capacity for carbon monoxide (DLCO; single breath) were performed in line with current guidelines and established reference values [13, 14]. Functional exercise capacity was assessed by the 6-min walking distance (6MWD) according to previous guidelines [15].

Physical Activity

We measured physical activity in patients with sarcoidosis for 1 week using the SenseWear Armband (BodyMedia, Inc., Pittsburgh, PA, USA). The armband is worn on the upper left arm over the triceps muscle and incorporates amongst other things a triaxial accelerometer that records the average number of steps per day; those are related to key functional characteristics and quality-of-life measures in chronic obstructive pulmonary disease [10, 16], asthma [17], idiopathic pulmonary fibrosis [8], and lymphangioleiomyomatosis [9]. We instructed the patients to wear the armband 24 h a day, except for the time spent on personal hygiene. We used a wearing time threshold of 94% (22.5 h) to identify valid days of physical activity measurement [16]. A monitoring period of 3–5 days has been shown to deliver reliable estimates of physical activity in free-living adult individuals [18]. In patients with chronic obstructive pulmonary disease of all severity grades, the validity of the measurement period has been evaluated, and a minimum of 5 days was able to achieve an intraclass correlation coefficient >0.8, irrespective of weekdays and disease severity [16]. Therefore, we applied this standardized and widely accepted methodological approach also to this cohort of patients with sarcoidosis. We defined physical inactivity as a daily number of steps <5,000, which is an established cutoff for a sedentary lifestyle [19].

Health-Related and Generic Quality of Life

The participants completed questionnaires for respiratory disease-specific quality of life (St George's Respiratory Questionnaire [SGRQ]) [20] and generic quality of life (12-Item Short-Form Health Survey [SF-12]) [21] during the study visit.

Fatigue

We assessed fatigue by the Multidimensional Fatigue Inventory (MFI-20) [22], a standardized questionnaire that has previously been validated in patients with sarcoidosis [23, 24]. The MFI is a 20-item self-reported questionnaire that covers the following 5 subscales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Each subscale covers 4 items rated on a 5-point Likert scale with 2 positively and 2 negatively formulated questions. The items are summed to subscale scores ranging from 4 to 20, resulting in a total score ranging from 20 to 100, with higher scores indicating more fatigue [25]. Age-specific norm values were derived from a German general population sample [26], with the 75th percentile as the cutoff for mild-to-moderate fatigue, and the 90th percentile as the cutoff for severe fatigue, as previously described [27].

Statistical Analysis

Descriptive data are reported as mean and standard deviation (continuous variables), median and interquartile range (categorical variables and continuous variables with skewed distribution), or number and percent (dichotomous variables), as appropriate.

Table 1. Sarcoidosis patient characteristics (*n* = 57)

<i>Demographics</i>	
Age, years	49.7±10.6
Male	32 (56%)
BMI	27.4±4.8
Pulmonary manifestations	53 (93%)
Chest radiography stages 0 + I	10 (18%)
Chest radiography stage II	44 (77%)
Chest radiography stages III + IV	3 (5%)
Extrapulmonary manifestations	43 (75%)
ACE titer, IU/L	56 (37–96)
<i>Therapy</i>	
Patients taking prednisone	30 (53%)
Prednisone, mg/day	10.8±13.9
Patients taking additional immunosuppressant therapy	9 (16%)
<i>Lung function and exercise capacity</i>	
FVC, % predicted	91.0±21.0
FEV ₁ , % predicted	82.7±20.8
FEV ₁ /FVC, %	0.75±0.08
DLCO, % predicted	73.1±15.1
6MWD, m	525±85
<i>Physical activity</i>	
Steps per day	7,490±3,007
<i>Health-related and generic quality of life</i>	
SGRQ score	24.7 (10.6–40.9)
SF-12 physical health score	43.2±10.7
SF-12 mental health score	49.3±10.2
<i>Fatigue</i>	
MFI-20, total score	48 (30–64)
No fatigue	32 (56%)
Mild-to-moderate fatigue	11 (19%)
Severe fatigue	14 (25%)
MFI-20, subscores	
General fatigue	12 (8–17)
Physical fatigue	10 (6–14)
Reduced activity	9 (6–13)
Reduced motivation	7 (4–9)
Mental fatigue	8 (4–12)

Data are presented as mean ± SD, median (IQR), or *n* (%), depending on the scale and distributional characteristics. Cutoffs for mild-to-moderate and severe fatigue are derived from the 75th and 90th percentiles of the general population in Germany, aged 40–59 years [26]. Data were missing for ACE (*n* = 34), DLCO (*n* = 1), SGRQ (*n* = 5), and SF-12 (*n* = 4). Reference range for ACE: 20–70 IU/L. BMI, body mass index; ACE, angiotensin-converting enzyme; FVC, forced vital capacity; FEV₁, forced expiratory volume at 1 s; DLCO, transfer factor of the lung for carbon monoxide; 6MWD, 6-min walking distance; SGRQ, St George's Respiratory Questionnaire; SF-12, 12-Item Short Form Health Survey; MFI-20, Multidimensional Fatigue Inventory.

We performed bivariate correlations between steps per day and established clinical parameters in patients with sarcoidosis (i.e., FVC, FEV₁, DLCO, 6MWD, SGRQ, SF-12, and MFI-20), reporting Pearson's correlation coefficient for normally distributed variables, and Spearman's ρ for nonnormally distributed variables. In order to compare the clinical meaning of physical activity and exercise capacity, we performed similar bivariate correlations replacing steps per day with 6MWD. We further explored the distribution of steps per day in relation to quartiles of the clinically most relevant parameters including exercise capacity (i.e., 6MWD), quality of life (i.e., SGRQ and SF-12 [physical health]), and fatigue (i.e., MFI-20 total score and MFI-20 subscore general fatigue). In a final step, we performed separate multivariate linear regression analyses, using steps per day as the dependent variable and significant clinical parameters as predictors, after adjusting for possible confounders (i.e., age, sex, and obesity [BMI ≥30]), and extrapulmonary organ involvement).

According to the prespecified cutoff for physical inactivity (i.e., number of steps <5,000), we then tested the predictive value of the clinically most relevant variables (i.e., 6MWD, as well as SGRQ and SF-12 physical health scores) and also explored the different domains of fatigue (i.e., MFI-20 total score and MFI-20 subscores). Therefore, we calculated the corresponding AUROC curves.

A *p* value <0.05 was considered to be statistically significant. Data analysis was performed with the Statistical Package for the Social Sciences version 20.0 (SPSS, Chicago, IL, USA).

Results

In total, we enrolled 59 patients with sarcoidosis in this study. We had to exclude 2 patients from the final analyses, due to incomplete physical activity data.

The studied population consisted of 57 patients with sarcoidosis (mean age 50 years, 56% male, mean FVC 91% predicted, mean DLCO 73% predicted) (Table 1). Exercise capacity was rather preserved (mean 6MWD 525 m), and 47% of the patients currently did not use any immunosuppressive therapy. The average number of steps per day in our study population was 7,490. The patients with extrapulmonary involvement showed a trend towards fewer steps when compared to those with lung involvement only (7,113 ± 2,614 vs. 8,649 ± 3,865; *p* = 0.082). The total MFI-20 score indicated mild-to-moderate fatigue in 19%, and severe fatigue in 25% of the patients. Data on the angiotensin-converting enzyme (ACE) titer were available for 23 patients (40.4%) (Table 1). Among these patients, the median ACE titer was in the normal range, and only 10 patients (43.5%) had ACE levels >70 IU/L.

On a bivariate level, exercise capacity (i.e., 6MWD), respiratory disease-specific quality of life (i.e., SGRQ score), and generic quality of life (i.e., SF-12 physical

health score) showed clear associations with steps per day ($p \leq 0.001$) (Table 2). The relationships between physical activity and fatigue were less clear, as only the MFI-20 subscales “physical fatigue” and “reduced activity”

Table 2. Bivariate correlations between clinical variables and steps per day or 6MWD in patients with sarcoidosis

Variable	Steps per day		6MWD	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
FVC (% predicted)	0.02	0.84	0.346	0.008
FEV ₁ (% predicted)	−0.06	0.66	0.23	0.085
DLCO (% predicted)	0.182	0.18	0.326	0.014
6MWD (m)	0.499	<0.001	n/a	n/a
Steps per day	n/a	n/a	0.499	<0.001
SGRQ	−0.459	0.001	−0.540	<0.001
SF-12 physical health	0.467	<0.001	0.604	<0.001
SF-12 mental health	0.111	0.429	0.132	0.345
MFI-20 total score	−0.259	0.052	−0.283	0.033
<i>MFI-20 subscores</i>				
General fatigue	−0.254	0.057	−0.256	0.055
Physical fatigue	−0.274	0.039	−0.294	0.027
Reduced activity	−0.277	0.037	−0.259	0.052
Reduced motivation	−0.208	0.120	−0.338	0.010
Mental fatigue	−0.122	0.364	−0.183	0.172

Bold type denotes significance. For SGRQ and MFI-20, Spearman’s ρ is reported. FVC, forced vital capacity; FEV₁, forced expiratory volume at 1 s; DLCO, transfer factor of the lung for carbon monoxide; 6MWD, 6-min walking distance; SGRQ, St George’s Respiratory Questionnaire; SF-12, 12-Item Short Form Health Survey; MFI-20, Multidimensional Fatigue Inventory.

showed some weak but statistically significant associations with the number of steps per day ($p < 0.05$), while the other subscales and the total score did not. Just like physical activity, 6MWD showed robust associations with SGRQ and SF-12 (physical health) scores ($p < 0.001$), and weak associations with fatigue. In contrast to physical activity, 6MWD was also significantly associated with lung function (i.e., FVC % predicted and DLCO % predicted; $p < 0.05$) (Table 2).

The distribution of steps per day across the quartiles for 6MWD and SGRQ, SF-12 physical health, and MFI-20 total scores is shown in Figure 1. The differences in steps per day between the patients in the highest and those in the lowest quartile were statistically significant for 6MWD, SGRQ score, and SF-12 physical health score ($p < 0.05$), but not for MFI-20 total score (Fig. 1). For the MFI-20 subscores, we performed similar analyses, and just as for the total score, we did not find any significant differences across quartile categories of steps per day (data not shown).

In the multivariate linear regression analyses adjusting for age, sex, obesity, and presence of extrapulmonary manifestations, using steps per day as the dependent variable, the associations between steps per day and 6MWD, SGRQ score, and SF-12 physical health score remained statistically significant (Table 3).

6MWD, SGRQ score, and SF-12 physical health score were able to identify physically inactive patients with good diagnostic accuracy (Table 4; Fig. 2). The MFI-20 subscore “general fatigue” was the only domain of fatigue that was able to identify physically inactive patients, even if only with poor diagnostic accuracy (Table 4; Fig. 2).

Table 3. Separate multivariate regression analyses with exercise capacity and quality of life as independent predictors of steps per day in patients with sarcoidosis after adjustment for basic confounders

Model	Predictive parameter	Standardized coefficient β	95% confidence interval	R^2 change	Total R^2	<i>p</i> value
A	6MWD (m)	0.42	6 to 24	0.14	0.34	0.002
B	SGRQ	−0.34	−1,701.4 to −164.7	0.10	0.27	0.02
C	SF-12 physical health	0.37	29.1 to 175.5	0.11	0.35	0.007

Bold type denotes significance. Interpretation: the additional effect of clinical parameters (i.e., exercise capacity and quality of life), independent of confounders (i.e., age, sex, obesity [BMI ≥ 30], and presence of extrapulmonary manifestations), was tested. Due to skewed distribution, the SGRQ score was log transformed. R^2 change reflects the additional effect of exercise capacity (A: 6MWD), health-related quality of life (B: SGRQ), and generic quality of life (C: SF-12 physical health), beyond the basic confounders. Total R^2 reflects variance explanation of the whole separate regression models, including the effect of confounders. 6MWD, 6-min walking distance; SGRQ, St George’s Respiratory Questionnaire; SF-12, 12-Item Short Form Health Survey.

Discussion

The main findings of our study are that exercise capacity, respiratory disease-specific quality of life, and generic quality of life are significantly associated with physical activity in patients with sarcoidosis. Different domains of fatigue also showed significant associations with physical

activity in these patients, but the relationships were surprisingly loose, and fatigue did not reliably detect physically inactive patients.

In sarcoidosis, the presence of exercise limitation may have significant clinical and therapeutic consequences [28, 29]. The self-paced 6-min walk test assesses a sub-maximal level of functional capacity, and may best reflect

Fig. 1. Distribution of the number of steps per day (mean $7,490 \pm 3,007$) across the quartiles of 6-min walking distance (6MWD) (**a**), St George's Respiratory Questionnaire (SGRQ) score (**b**), 12-Item Short Form Health Survey (SF-12) physical health score (**c**), and Multidimensional Fatigue Inventory (MFI-20) total score (**d**) in patients with sarcoidosis. Most impaired patients may be represented either in the lowest quartile (6MWD and SF-12; **a**, **c**) or in the highest quartile (SGRQ and MFI-20; **b**, **d**), and in both cases are displayed rightmost in the respective graphs. Whiskers repre-

sent the mean $\pm$ standard error for each quartile of each variable. ANOVAs were performed to compare steps per day between the quartiles of the single variables. Differences in steps per day between patients in the highest and those in the lowest quartile were statistically significant for 6MWD ($8,725 \pm 1,989$ vs. $4,737 \pm 2,329$ steps; $p < 0.001$), SGRQ ($9,275 \pm 2,903$ vs. $5,743 \pm 2,927$ steps; $p = 0.003$), and SF-12 physical health ($8,452 \pm 2,856$ vs. $5,462 \pm 2,664$ steps; $p = 0.008$), but not for MFI-20 total score ($8,145 \pm 2,732$ vs. $6,068 \pm 3,011$; $p = 0.065$).

daily physical activity levels when compared to other walk tests [15, 30]. In our study, the distance walked in the 6-min walk test was the strongest predictor of physical activity, and identified physically inactive patients with excellent diagnostic accuracy. The close association of ex-

ercise capacity and physical activity in our study sample seems to be mainly driven by patients with meaningful reductions of their functional status. In patients with a 6MWD below 480 m (i.e., approx. the 10th percentile of the general population [31]), the corresponding number

Fig. 2. ROC curves for 6-min walking distance (6MWD) (**a**), St George's Respiratory Questionnaire (SGRQ) score (**b**), 12-Item Short Form Health Survey (SF-12) physical health score (**c**), and Multidimensional Fatigue Inventory (MFI-20) subscore "general

fatigue" (**d**), identifying patients with significantly reduced physical activity (i.e., <5,000 steps per day; $n = 13$ patients). The corresponding AUROC curves were 0.90, 0.81, 0.80, and 0.70, respectively ($p < 0.001$, 0.002, 0.003, and 0.03, respectively).

Table 4. ROC curves for 6MWD, SGRQ, SF-12 physical health, and MFI-20 as predictors of a low number of steps per day (<5,000)

Variable	AUROC	p value
6MWD (m)	0.90	<0.001
SGRQ	0.81	0.002
SF-12 physical health	0.80	0.003
MFI-20 total score	0.67	0.06
<i>MFI-20 subscores</i>		
General fatigue	0.70	0.03
Physical fatigue	0.67	0.06
Reduced activity	0.66	0.07
Reduced motivation	0.63	0.17
Mental fatigue	0.60	0.30

Bold type denotes significance. Interpretation: separate ROC curves were performed and AUROC calculated, using 5,000 steps per day as the clinical cutoff for significantly reduced physical activity. 6MWD, SGRQ, SF-12 physical health, MFI-20 total score, and MFI-20 subscores (i.e., general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) served as predictors. 6MWD, SGRQ, and SF-12 physical health identified physically inactive patients ($n = 13$) with proper diagnostic accuracy. The MFI-20 subscore “general fatigue” was the only domain of fatigue that was able to identify physically inactive patients with sarcoidosis, albeit with a rather poor diagnostic accuracy. 6MWD, 6-min walking distance; SGRQ, St George’s Respiratory Questionnaire; SF-12, 12-Item Short Form Health Survey; MFI-20, Multidimensional Fatigue Inventory.

of steps per day was as low as 4,700. Therefore, measures of daily physical activity might assist clinicians in the functional evaluation of their patients, and identify those patients that are potentially harmed by their disease.

In our study, the average number of steps per day among patients with sarcoidosis was about 7,500, which is very similar to that among patients with mild-to-moderate asthma with comparable demographics (i.e., 7,831), but probably also not significantly reduced when compared to a healthy population (i.e., 8,912) [17]. Most of the patients in our cohort regularly visited our outpatient tertiary care center after an acute onset of sarcoidosis requiring immuno-suppressive therapy and/or for second opinion, and showed minimal impairments of lung function or exercise capacity only. The generally preserved functional status and low disease activity of our study population might explain the rather normal levels of daily physical activity, even though exercise capacity and lung function showed some associations in our study. Relationships between lung function and exercise capacity have previously been reported in other cohorts [32].

Our results indicate that mild lung functional impairments in patients with sarcoidosis might not have clinically significant negative effects on daily physical activity, despite its consequences being already measurable in exercise tests.

Clinicians taking care of patients with sarcoidosis increasingly recognize changes to health-related and generic quality of life as clinically meaningful assessment parameters [2]. Our study is the first to link these patient-reported measures to objective measures of daily physical activity. The average number of steps per day was reduced by more than one-third across the quartiles of SGRQ or SF-12 scores. Furthermore, the associations we found were independent of confounders, indicating a robust relationship. Interestingly, each parameter explained about 25% of the variance of steps per day in patients with sarcoidosis, which is quite remarkable given the number of non-disease-related confounders of physical activity in patients with rather preserved functional status.

In contrast to our initial hypothesis, measures of fatigue showed rather loose and partly inconsistent associations with physical activity in patients with sarcoidosis. Fatigue is a frequent clinical manifestation of sarcoidosis, largely unrelated to measures of exercise capacity and lung function, and often unaffected by immunosuppressive therapy [6, 7, 33]. However, high levels of fatigue have a significant adverse impact on the patient’s quality of life [34, 35]. This means that fatigue in sarcoidosis is a complex, unexplained syndrome with large discrepancies when objective and subjective consequences are studied. In patients with otherwise not specified chronic fatigue syndrome, even minor physical exertions increase the fatigue symptoms and lead to a more sedentary lifestyle, suggesting that the same might be true for patients with sarcoidosis [36, 37]. However, in a previous study in patients with sarcoidosis, Korenromp et al. [12] did not find clear differences in physical activity when patients with fatigue were compared with those without fatigue. Looking at the bivariate correlations in our study, the “reduced activity” domain and the “physical fatigue” domain of the MFI-20 in fact were weakly associated with reduced physical activity, supporting the validity of these items. However, the item “general fatigue” was the only domain of the MFI-20 that successfully identified sedentary patients, even though its diagnostic accuracy was relatively poor when compared with the exercise capacity and quality of life assessments. Our findings suggest that in patients with sarcoidosis, fatigue is not the predominant factor associated with physical activity impairment. The presence of milder forms of fa-

tigue therefore might not preclude patients from being physically active, although this symptom is subjectively perceived as highly disabling.

Limitations of our study are the rather small size of the sample with a generally rather preserved lung functional status, the lack of ACE titers in the majority of patients, and the fact that we did not use the recently published King's Sarcoidosis Questionnaire as a disease-specific health status assessment, which is currently validated English and Dutch only [38, 39]. In addition, one might argue that the rather loose associations of fatigue and physical activity might be biased by the relatively large proportion of patients that had fatigue scores within the normal range. However, even though the cohort covers the whole spectrum of fatigue, including 25% patients with severe fatigue, we still did not find any significant differences in physical activity between the highest and the lowest quartile of fatigue. Furthermore, the correlation coefficients that we found between fatigue and exercise capacity are comparable to those of other cohort studies [5, 6], which indicates that our cohort is a representative sample that adequately represents the clinical consequences of the disease. There also might be concerns that in individuals with only mild functional impairments, non-disease-associated factors might increasingly impact daily physical activity, and therefore the

measurement period should be prolonged. However, the methodological approach applied in this study is well established in health and disease, and a longer duration might as well result in lower compliance to wear the arm-band, and consequently a lower number of valid consecutive measurement days.

Conclusion

The results of our study suggest that exercise capacity and quality of life measures are robust and clinically meaningful predictors of daily physical activity in patients with sarcoidosis. In contrast, fatigue showed minor associations with physical activity only, although being perceived as highly disabling by the patients. Therefore, milder forms of fatigue might not preclude patients from being physically active.

Acknowledgement

We are thankful to Daniela Beissel for her excellent support in study logistics, and to Marco Gramm for his support in data management. The work was supported by the Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL e.V.).

References

- 1 Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999;160:736–755.
- 2 Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J: Sarcoidosis. *Lancet* 2014;383:1155–1167.
- 3 de Kleijn WP, De Vries J, Lower EE, Elfferich MD, Baughman RP, Drent M: Fatigue in sarcoidosis: a systematic review. *Curr Opin Pulm Med* 2009;15:499–506.
- 4 Drent M, Strookappe B, Hoitsma E, De Vries J: Consequences of sarcoidosis. *Clin Chest Med* 2015;36:727–737.
- 5 Strookappe B, De Vries J, Elfferich M, Kuijpers P, Knevel T, Drent M: Predictors of fatigue in sarcoidosis: the value of exercise testing. *Respir Med* 2016;116:49–54.
- 6 Marcellis RG, Lenssen AF, Elfferich MD, De Vries J, Kassim S, Foerster K, Drent M: Exercise capacity, muscle strength and fatigue in sarcoidosis. *Eur Respir J* 2011;38:628–634.
- 7 De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M: The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21:127–136.
- 8 Bahmer T, Kirsten AM, Waschki B, Rabe KF, Magnussen H, Kirsten D, Gramm M, Hummiller S, Brunnemer E, Kreuter M, Watz H: Clinical correlates of reduced physical activity in idiopathic pulmonary fibrosis. *Respiration* 2016;91:497–502.
- 9 Bahmer T, Watz H, Waschki B, Gramm M, Magnussen H, Rabe KF, Wirtz H, Kirsten D, Kirsten A: Reduced physical activity in lymphangioleiomyomatosis compared with COPD and healthy controls: disease-specific impact and clinical correlates. *Thorax* 2016;71:662–663.
- 10 Waschki B, Spruit MA, Watz H, Albert PS, Shrikrishna D, Groenen M, Smith C, Man WD, Tal-Singer R, Edwards LD, Calverley PM, Magnussen H, Polkey MI, Wouters EF: Physical activity monitoring in COPD: compliance and associations with clinical characteristics in a multicenter study. *Respir Med* 2012;106:522–530.
- 11 Saligan LN: The relationship between physical activity, functional performance and fatigue in sarcoidosis. *J Clin Nurs* 2014;23:2376–2378.
- 12 Korenromp IH, Heijnen CJ, Vogels OJ, van den Bosch JM, Grutters JC: Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. *Chest* 2011;140:441–447.
- 13 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J: Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
- 14 MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26:720–735.

- 15 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166:111–117.
- 16 Watz H, Waschki B, Meyer T, Magnussen H: Physical activity in patients with COPD. *Eur Respir J* 2009;33:262–272.
- 17 Bahmer T, Waschki B, Schatz F, Herzmann C, Zabel P, Kirsten AM, Rabe KF, Watz H: Physical activity, airway resistance and small airway dysfunction in severe asthma. *Eur Respir J* 2017;49:1601827.
- 18 Trost SG, McIver KL, Pate RR: Conducting accelerometer-based activity assessments in field-based research. *Med Sci Sports Exerc* 2005;37:S531–S543.
- 19 Tudor-Locke C, Craig CL, Thyfault JP, Spence JC: A step-defined sedentary lifestyle index: <5,000 steps/day. *Appl Physiol Nutr Metab* 2013;38:100–114.
- 20 Swigris JJ, Esser D, Conoscenti CS, Brown KK: The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review. *Health Qual Life Outcomes* 2014;12:124.
- 21 Han MK, Swigris J, Liu L, Bartholmai B, Murray S, Giardino N, Thompson B, Frederick M, Li D, Schwarz M, Limper A, Flaherty K, Martinez FJ: Gender influences health-related quality of life in IPF. *Respir Med* 2010;104:724–730.
- 22 Smets EM, Garssen B, Bonke B, De Haes JC: The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; 39:315–325.
- 23 Hinz A, Fleischer M, Brähler E, Wirtz H, Bosse-Henck A: Fatigue in patients with sarcoidosis, compared with the general population. *Gen Hosp Psychiatry* 2011;33:462–468.
- 24 Fleischer M, Hinz A, Brähler E, Wirtz H, Bosse-Henck A: Factors associated with fatigue in sarcoidosis. *Respir Care* 2014;59: 1086–1094.
- 25 Smets EM, Garssen B, Cull A, de Haes JC: Application of the Multidimensional Fatigue Inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer* 1996;73:241–245.
- 26 Schwarz R, Krauss O, Hinz A: Fatigue in the general population. *Onkologie* 2003;26:140–144.
- 27 Kuhnt S, Ernst J, Singer S, Rüffer JU, Kortmann RD, Stolzenburg JU, Schwarz R: Fatigue in cancer survivors – prevalence and correlates. *Onkologie* 2009;32:312–317.
- 28 Wijsenbeek MS, Culver DA: Treatment of sarcoidosis. *Clin Chest Med* 2015;36:751–767.
- 29 Judson MA: The treatment of pulmonary sarcoidosis. *Respir Med* 2012;106:1351–1361.
- 30 Solway S, Brooks D, Lacasse Y, Thomas S: A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001;119:256–270.
- 31 Casanova C, Celli BR, Barria P, Casas A, Cote C, de Torres JP, Jardim J, Lopez MV, Marin JM, Montes de Oca M, Pinto-Plata V, Aguirre-Jaime A: The 6-min walk distance in healthy subjects: reference standards from seven countries. *Eur Respir J* 2011;37:150–156.
- 32 Baughman RP, Sparkman BK, Lower EE: Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007;132:207–213.
- 33 Atkins C, Wilson AM: Managing fatigue in sarcoidosis – a systematic review of the evidence. *Chron Respir Dis* 2017;14:161–173.
- 34 Drent M, Marcellis R, Lenssen A, De Vries J: Association between physical functions and quality of life in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2014;31:117–128.
- 35 Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J: Fatigue is associated with quality of life in sarcoidosis patients. *Chest* 2006;130: 989–994.
- 36 Vercoulen JH, Hommes OR, Swanink CM, Jongen PJ, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G: The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. *Arch Neurol* 1996;53:642–649.
- 37 Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G: Prognosis in chronic fatigue syndrome: a prospective study on the natural course. *J Neurol Neurosurg Psychiatry* 1996;60:489–494.
- 38 Patel AS, Siegert RJ, Creamer D, Larkin G, Maher TM, Renzoni EA, Wells AU, Higginson IJ, Birring SS: The development and validation of the King's Sarcoidosis Questionnaire for the assessment of health status. *Thorax* 2013;68:57–65.
- 39 Van Manen MJ, Wapenaar M, Strookappe B, Drent M, Elfferich M, de Vries J, Gosker HR, Birring SS, Patel AS, van den Toorn L, van den Blink B, Boomars K, Hoitsma E, Wijsenbeek MS: Validation of the King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population. *Sarcoidosis Vasc Diffuse Lung Dis* 2016;33:75–82.