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Fatigue in patients with inactive sarcoidosis does not correlate with lung ventilation ability or walking distance. Pilot Study

Zmęczenie u chorych z nieaktywną sarkoidozą nie koreluje ze zdolnością wentylacyjną płuc oraz z dystansem chodu. Badanie pilotażowe

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Abstract

Introduction: Fatigue is one of many symptoms reported by patients with sarcoidosis. It is believed that fatigue may be the cause of exercise intolerance and reduced quality of life in patients with sarcoidosis. The purpose of the work was to present the frequency of fatigue prevalence in patients with sarcoidosis and to investigate the correlation between fatigue and the results of pulmonary function tests and walking distance.

Material and methods: A total of 74 patients with sarcoidosis in a stable phase of the disease, not treated in the past with glucocorticoids or immunosuppressive drugs, and without indications for treatment at the time of the study were examined. In all patients fatigue evaluation was carried out with the use of the Fatigue Assessment Scale questionnaire (FAS); dyspnoea was assessed with the use of the Medical Research Council scale (MRC). Body Mass Index (BMI), spirometry, and a 6-minute walk test were additionally performed. The control group included 30 healthy volunteers who completed the FAS.

Results: In the examined group of patients fatigue was diagnosed in 36 patients (50%), and in 5 (6.94%) - strong fatigue was observed. The remaining 31 (43.06%) patients felt no fatigue. The average value of points obtained by FAS questionnaire in sarcoidosis patients was significantly higher than the respective value in the control group ($p = 0.02$). A significantly higher number of points by FAS questionnaire was observed in female patients with sarcoidosis ($p = 0.04$) in comparison to men. No significant statistical correlation between fatigue index FAS and BMI ($r = 0.22$, $p = 0.11$), FEV_1 ($r = -0.11$, $p = 0.3$), $FEV_1\%$ pred. ($r = 0.01$, $p = 0.9$), FVC ($r = -0.03$, $p = 0.77$), FEF_{25-75} ($r = -0.23$, $p = 0.1$) and the distance in the six-minute walk test (6MWT) ($r = -0.01$, $p = 0.9$) was observed. However, there was a weak negative correlation between the age of the patients and the FAS index ($r = -0.29$, $p = 0.01$).

Conclusions: Fatigue in patients with sarcoidosis does not correlate with the results of lung function tests or with walking distance in 6MWT.

Key words: fatigue, sarcoidosis, pulmonary function tests, 6-minute walk test

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Streszczenie

Wstęp: Zmęczenie jest jednym z wielu zgłaszanych objawów u chorych na sarkoidozę. Uważa się, że zmęczenie może być przyczyną nietolerancji wysiłku fizycznego u chorych na sarkoidozę oraz obniżenia jakości życia. Celem pracy jest przedstawienie częstości występowania zmęczenia u chorych na sarkoidozę oraz zbadanie korelacji pomiędzy zmęczeniem a wynikami badań czynnościowych płuc i dystansem chodu.

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Materiał i metody: Zbadano 74 chorych na sarkoidozę w stabilnym okresie choroby, nieleczonych w przeszłości glikokortykoidami lub lekami immunosupresyjnymi i bez wskazań do leczenia w chwili badania. U wszystkich chorych dokonano oceny zmęczenia kwestionariuszem FAS (*Fatigue Assessment Scale*), oceniono duszność za pomocą skali MRC (*Medical Research Council*). Zbadano również wskaźnik masy ciała BMI (*body mass index*) oraz dokonano oceny spirometrycznej oraz przeprowadzono 6-minutowy test chodu. Badaniem objęto również 30 zdrowych ochotników, u których dokonano oceny zmęczenia (FAS).

Wyniki: W badanej grupie chorych stwierdzono zmęczenie u 36 (50%), a u 5 (6,94%) bardzo duże zmęczenie. Pozostałych 31 (43,06%) pacjentów nie odczuwało zmęczenia. Średnia wartość uzyskanych punktów wg kwestionariusza FAS u chorych na sarkoidozę była istotnie wyższa niż obserwowana wartość w grupie kontrolnej ($p = 0,02$). Istotnie większą liczbę punktów według kwestionariusza FAS obserwowano u kobiet chorych na sarkoidozę ($p = 0,04$) w porównaniu z mężczyznami. Nie stwierdzono istotnych statystycznie zależności pomiędzy wskaźnikiem zmęczenia FAS a BMI ($r = 0,22$, $p = 0,11$), FEV₁ ($r = -0,11$, $p = 0,3$), FEV₁% pred. ($r = 0,01$, $p = 0,9$), FVC ($r = -0,03$, $p = 0,77$), FEF_{25–75} ($r = -0,23$, $p = 0,1$) oraz dystansem w teście sześciominutowego marszu ($r = -0,01$, $p = 0,9$). Stwierdzono natomiast słabą ujemną korelację między wiekiem badanych chorych a wskaźnikiem FAS ($r = -0,29$, $p = 0,01$).

Wnioski: Zmęczenie u chorych na sarkoidozę nie wpływa na dystans chodu i na zdolność wentylacyjną płuc.

Słowa kluczowe: zmęczenie, sarkoidoza, testy czynnościowe płuc, 6-minutowy test marszu

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Introduction

Sarcoidosis is a multiorgan disorder that is characterised by the formation of noncaseating granulomas in many different organs. The disease often (in 80–90% of patients) involves the lungs and lymph nodes located in the chest [1, 2]. It affects mainly young people between 25 and 35 years of age [1].

Clinical signs of sarcoidosis are generally nonspecific. The most frequent complaints reported by Caucasian patients, include: dyspnoea (approximately 50% of patients), exercise intolerance (58% of patients), muscular pain (29%), and ocular problems (about 25%) [1, 2]. Fever as a nonspecific sign is observed in as many as 32% of patients [3].

Cough, muscular, chest and joint pains, or weight loss are non-specific signs, which may be present also in other systemic or neoplastic diseases [4, 5]. Clinical signs of the disease and the number of extrathoracic organs involved differ significantly between Caucasian, Afro-American, or Asian patients [5].

According to many authors, one of the symptoms most frequently reported by patients with sarcoidosis but underrated by doctors, is fatigue, which may occur even in 30 to 90% of patients [4, 6, 7].

Fatigue is a subjective symptom reported not only by patients with sarcoidosis but also by patients with neoplastic, infectious, and rheumatologic diseases [2, 8]. It is described as a sensation of overwhelming strength reduction, lack of energy and the feeling of complete exhaustion [2, 9, 10]. It may be experienced at rest and it usually increases under stress over the course of the day. Fatigue frequently coexists with depression, from

which it differs in the lack of lowered self-evaluation, despair, and the sense of hopelessness [2, 9, 10].

Fatigue may substantially influence everyday functioning of patients, *inter alia*, their occupational and social life or physical activity [2]. It is believed that fatigue and general strength reduction of the organism may cause exercise intolerance and lower the quality of life in sarcoidosis patients [8, 11]. The majority of patients complain of concomitant fatigability of the lower extremities [8].

The aim of the study was to present the prevalence of fatigue in patients with stable sarcoidosis not treated with glucocorticoids, and to investigate correlation between fatigue and lung function test results and exercise capacity.

In Poland, research into the occurrence of fatigue in patients with sarcoidosis has not been carried out to date; neither has the influence of fatigue on exercise tolerance and patients' activity has been defined.

Material and methods

The study included 74 patients with sarcoidosis (21 women and 53 men) aged 29–71 years (the mean age 45.3 years), who reported to the Outpatient Clinic of the Hospital for Lung Diseases and Tuberculosis in Zabrze in the period from 01.06.2008 to 01.08.2008 and from 01.01.2010 to 01.03.2010. None of the women participating in the research was pregnant at the time of the study. Sarcoidosis was diagnosed earlier at the Teaching Hospital of Lung Diseases and Tuberculosis in Zabrze in accordance with the criteria of the American Thoracic Society/World Asso-

Table 1. General characteristics of treated and control group

	Treated group	Control group
Total (n)	74	30
Women (n)	21	15
Men (n)	53	15
Age (yrs)	43.5 (29–71)	49.7 (29–68)
Stage of sarcoidosis:		
I	21	
II	23	
III	24	
BMI (kg/m ²)	26.6	25.2
FAS (points) mean/SD	22.9 ± 7.3 SD	18.1 ± 4.3 SD
FEV ₁ (l) mean/SD	3.18 ± 0.82 SD	
FEV ₁ % pred. mean/SD	90.4 ± 13.1 SD	
FVC (l) mean/SD	4.16 ± 1.1 SD	
FVC % pred. mean/SD	98.9 ± 13.9 SD	
FEV ₁ /FVC(%) mean/SD	95 ± 9.6 SD	
FEF _{25–75} (l/s) mean/SD	3.7 ± 1.2 SD	
FEF _{25–75} % pred. mean/SD	89.4 ± 26.5 SD	
6MWT (m) mean/SD	555.9 ± 91.5 SD	
MRC (points) mean/SD	1.21 ± 0.8 SD	

All abbreviations in the text

ciation for Sarcoidosis and Other Granulomatous Disorders (ATS/WASOG) [1]. The study group consisted of 21 patients at radiological stage I, 23 at stage II, and 24 at stage III of sarcoidosis. None of the patients smoked cigarettes. According to the available documentation, the duration of sarcoidosis did not exceed four years. Only the patients at a stable stage of the disease, not treated in the past with glucocorticoids or immunosuppressive drugs, and with no indications for treatment according to the ATS/WASOG criteria during the examination, entered the study. No symptoms of extrapulmonary sarcoidosis or other chronic concomitant disorders or signs of acute infection were observed in the patients during the period of at least three months prior to the study.

In all patients, dyspnoea was evaluated using the MRC scale [12], and fatigue — with the help of the Polish version of the Fatigue Assessment Scale (FAS), calculating the so-called “FAS index” [6]. The authors of the FAS gave their consent for use of the scale in the present study.

We measured fatigue with the help of the FAS questionnaire, which is used more often and is more objective than other questionnaires, such as: the Energy and Fatigue Scale of the World Health Organization Quality of Life Assessment Instru-

ment — 100 (WHOQOL-100), Fatigue Scale (FS), and Functional Assessment of Chronic Illness Therapy — Fatigue (FACIT-F) [15].

The FAS questionnaire includes 10 questions concerning the frequency of physical and mental fatigue during the previous year (Table 1). There are five possible answers to the questions: “never, sometimes, regularly, often, and always”, which are evaluated on a scale from 1 to 5.

The results of the FAS were classified as: no fatigue (10–21 points), fatigue (22–34 points), and very strong fatigue (35–50 points) [6].

In all of the patients from the present study, BMI was calculated and spirometry was performed, using Lungtest apparatus produced by MES (MES-SC Kraków Poland), in accordance with the ATS/ERS guidelines and Polish guidelines for spirometry [PTCHP (*Polish Society of Lung Diseases*) 2006 [13]. The obtained results of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and forced expiratory flow (FEF_{25–75}) were expressed as a percentage of predicted values according to Quanjer et al. [14]. Additionally, in accordance with the guidelines of the American Thoracic Society of 2002 [15], a 6-minute walk test (6MWT) was performed.

Table 2. Fatigue Assessment Scale

	Never	Sometimes	Regular	Often	Always
1. I am bothered by fatigue	1	2	3	4	5
2. I get tired very quickly	1	2	3	4	5
3. I don't do much during the day	1	2	3	4	5
4. I have enough energy for everyday life	1	2	3	4	5
5. Physically, I feel exhausted	1	2	3	4	5
6. I have problems to start things	1	2	3	4	5
7. I have problems to think clearly	1	2	3	4	5
8. I feel no desire to do anything	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, i can concentrate quite well	1	2	3	4	5

Fatigue was also measured using the FAS questionnaire in a control group of 30 healthy volunteers. The control group consisted of 15 men and 15 women. No one from the control group reported any concomitant diseases. The group of healthy volunteers did not undergo any other diagnostic tests.

The study was approved by the Bioethics Committee of the Medical University of Silesia.

Statistical evaluation of the obtained results, after examining normal distribution, was conducted using one-way analysis of variance, the Kruskal-Wallis test, and non-parametric Wilcoxon test. The relation between the variables was evaluated using Pearson and Spearman correlation analysis. Multiple regression analysis was also applied. $P < 0.05$ was assumed as statistically significant.

Results

Demographic data and mean values of the results obtained in the FAS and function tests outcome are presented in Table 2.

According to the FAS, 36 (50%) sarcoidosis patients felt fatigue, and 5 (6.94%) — strong fatigue. The remaining 31 (43.06%) patients did not feel fatigue. In the control group, 7 (23.33%) healthy individuals reported fatigue, and the remaining 21 (76.67%) were free from this symptom.

The mean FAS score in patients with sarcoidosis was significantly higher than the FAS score in the control group ($p = 0.02$). FAS score was significantly higher in females than in males ($p = 0.04$) (Fig. 1). The mean number of points obtained from the FAS was not significantly different in patients at stage I, II, or III of sarcoidosis (Fig. 2).

No statistically significant correlations were found between the FAS index and BMI.

There was no significant correlation between the FAS index and lung function tests results (Figs 3–5). They were: for FEF_{25-75} ($r = 0.23$, $p = 0.1$), for FEV_1 ($r = 0.05$, $p = 0.96$), and for FVC ($r = 0.03$, $p = 0.77$).

No correlation between 6-minute walking distance and FAS score was found either ($r = 0.01$, $p = 0.9$) (Fig. 6).

However, a weak negative correlation between the age of the examined patients and the FAS index was found ($r = -0.29$, $p = 0.02$) (Fig. 7). In the group of healthy subjects, no statistically significant differences were found between the age of the examined individuals and the FAS index ($r = 0.3$, $p = 0.09$).

Discussion

No correlation between fatigue and lung ventilation ability or exercise tolerance measured with a 6-minute walk test was found in the examined patients, which suggests that fatigue does not have an impact on exercise tolerance.

Using the FAS questionnaire in the selected group of ambulatory patients with chronic, stable sarcoidosis in remission, we observed fatigue in 56.94% of the subjects. The study was not epidemiological, and it included a small number of selected patients with no indication for treatment. Hence, the obtained data cannot be compared with the results produced by other authors, whose studies were conducted on considerably greater groups of patients making up a complete clinical cross-section. According to data collected in Denmark, fatigue measured with the FAS was reported by as many as 71% out of

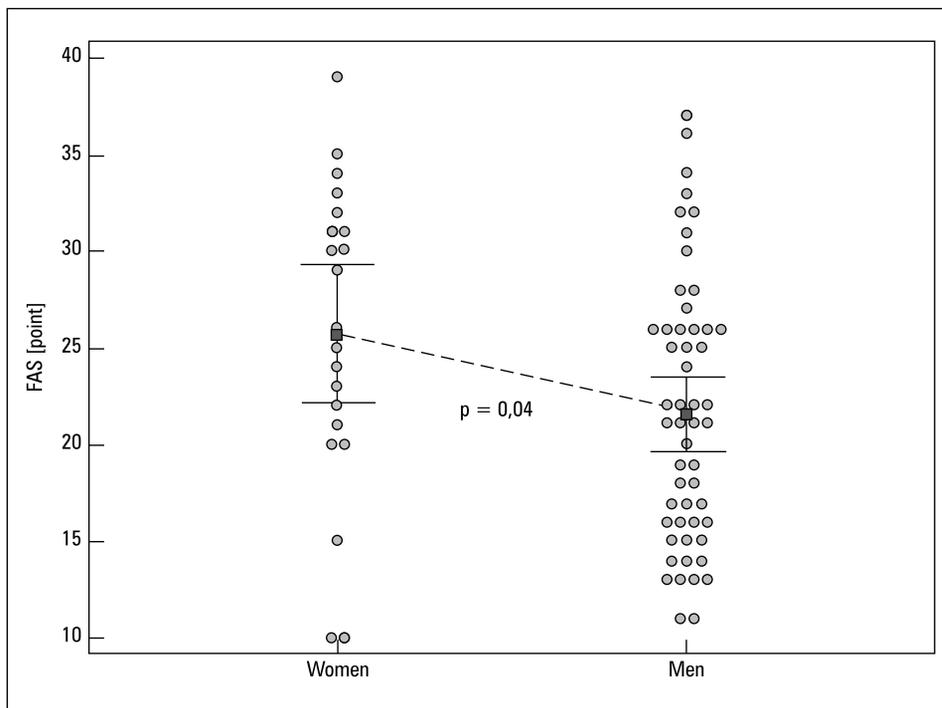


Figure 1. Comparison of the fatigue indicator FAS with gender

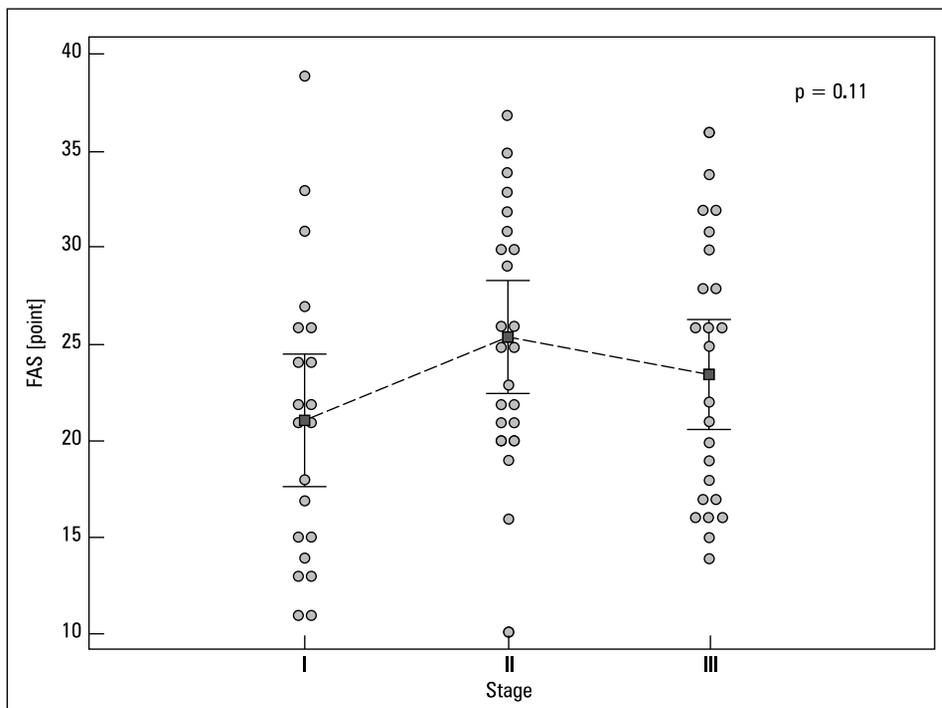


Figure 2. Comparison of the fatigue indicator FAS with disease stage

1,755 interviewed individuals [16, 17]. Fatigue was the most frequent symptom reported by patients with sarcoidosis of different degrees of activity [3]. Research carried out in Germany on 1,197 patients showed that nearly 62% of men

and 74% of women complained of fatigue [18]. Korenromp et al. in the Netherlands examined 75 patients with sarcoidosis, and 76% of them reported fatigue in the course of the disease. Yet, the patients were not examined with the help of

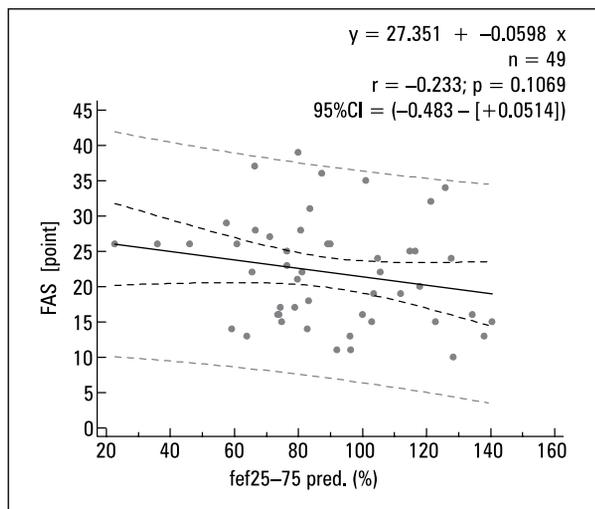


Figure 3. Correlation between the fatigue indicator FAS and the forced expiratory flow (FEF₂₅₋₇₅)

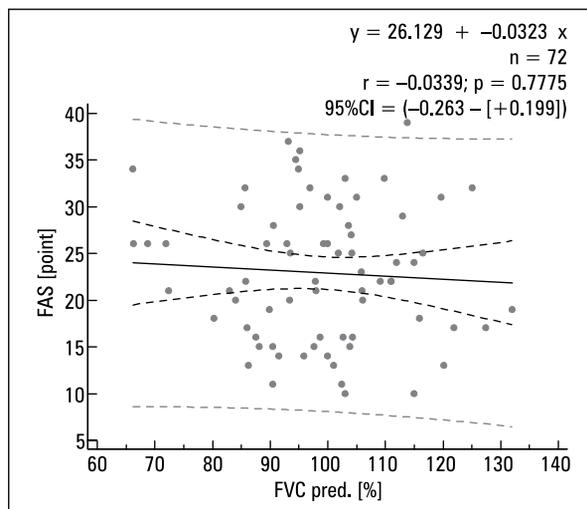


Figure 5. Correlation between the fatigue indicator FAS and the forced vital capacity (FVC)

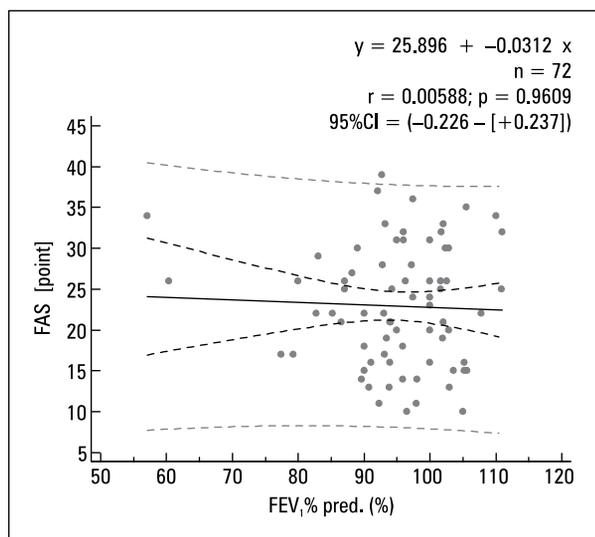


Figure 4. Correlation between the fatigue indicator FAS and forced expiratory volume in 1 second (FEV₁)

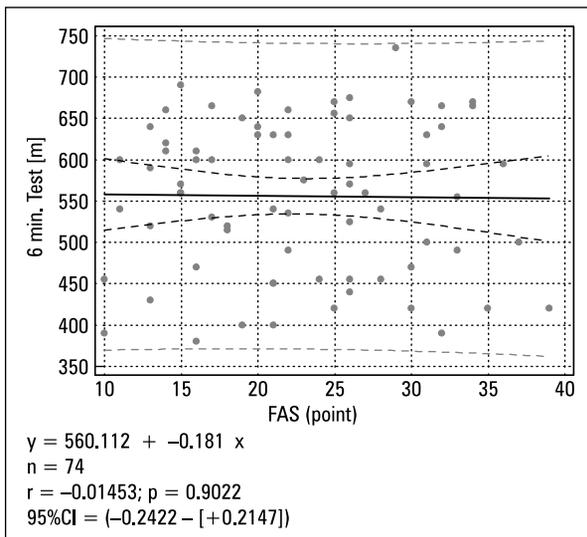


Figure 6. Correlation between the fatigue indicator FAS and the distance in 6-minute walk test

the FAS questionnaire but with the Checklist Individual Strength (CIS), Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and Symptom Checklist-90 (SCL-90) [19].

Among our patients, women also had a higher FAS index than men did, whereas BMI did not correlate with degree of fatigue measured with the FAS. Other authors indicated higher values of the FAS index in older patients, i.e. at the age of 51–60 years, which was confirmed by us in the present study.

In sarcoidosis, fatigue may be intensified by acute stage of the disease, obesity, or glucocorticoid use [20]. Sleep apnoea may also have some influence on fatigue sensation. Other possible

causes of fatigue in sarcoidosis include the following: inflammatory process with formation of sarcoidal granulomas, myopathy, concomitant chronic pain disorders, feeling of general strength reduction, depression, and small fibre neuropathy (SFN) [21]. However, the causes of fatigue in sarcoidosis have not been clearly determined [6, 9].

The research by Alhamad, Baughman, and Spruit [22, 23] showed that 73% of sarcoidosis patients in 6MWT covered a distance shorter than 400 m, and their exercise tolerance measured with this test is markedly lower than that of healthy individuals [22]. In the research by Miller [18, 24], 67% of patients stopped during the test due to “weakness of the lower extremities”,

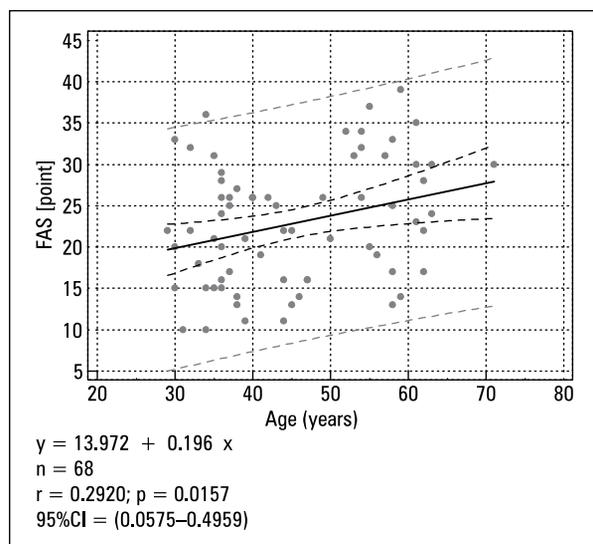


Figure 7. Correlation between the fatigue indicator FAS and patients' age

which was caused by weakness of muscles. The research carried out on 124 sarcoidosis patients by Marcellis confirmed shortening of the distance in a 6 MWT and reduced exercise tolerance in the patients. The strength of the quadriceps muscle of the thigh, of the palm muscles, and respiratory muscles was significantly lower in sarcoidosis compared to the control group. A correlation between muscle strength and fatigue was found to be weak in men and strong in the examined women [25]. The research conducted by Spruit showed that patients complaining of fatigue had lower muscle mass and lower exercise tolerance, compared to healthy subjects [11]. However, in the present study, fatigue measured with the FAS did not correlate with the distance in 6 MWT.

The research performed by Alhamad et al. between 2002 and 2008 on 59 sarcoidosis patients from three different centres in Saudi Arabia showed that women covered significantly shorter distances in 6-minute walk tests compared to men $p < 0.01$ [27].

Maimon et al., in the study carried out between 2009 and 2011, observed that sarcoidosis patients with pulmonary hypertension covered significantly shorter distance in a 6-minute walk test, $p < 0.01$ [27].

In the present study we found no correlation between the results of lung function tests and FAS score. Michelsen et al. did not find any correlation between the FAS score and spirometric parameters, nor between the FAS and radiological progression of sarcoidosis [9]. In the case of 150 patients examined by Michelsen et al. in Zagreb, the most frequently reported symptom was fatigue (59.5%) [28].

In Germany Kabitz conducted a 6-minute walk test on a small group of 24 sarcoidosis male patients. In comparison with the control group, the subjects covered significantly shorter distance $p = 0.025$, but fatigue was not evaluated by any questionnaire [30].

In our group of patients, there were no individuals with radiological or functional progression, which markedly intensifies the sensation of fatigue [3]. However, we did not analyse the impact of social factors such as education or profession on fatigue sensation. According to some authors, active professional work and regular physical exercise decrease depression, strength reduction, and the feeling of fatigue in chronic diseases of the respiratory system [8].

Conclusions

In the study group, no correlation was found between fatigue and walking distance or lung ventilation ability. The cause of fatigue in patients with sarcoidosis remains unknown and the problem undoubtedly needs further research.

Conflict of interest

The authors declare no conflict of interest.

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