Chapter 2

Reduced muscle strength, exercise intolerance and disabling symptoms in sarcoidosis

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Abstract

Purpose of review

This review focuses on innovations in the field of assessment and treatment of muscle weakness and exercise intolerance in sarcoidosis and the association between these and fatigue, dyspnea and quality of life (QoL).

Recent findings

Muscle strength and exercise intolerance are prevalent in patients with sarcoidosis. Exercise testing can be used to identify the presence of strength deficits and exercise intolerance. Routinely performed clinical tests, including lung function tests and imaging methods, are only weakly related to these nonspecific health complaints. Assessment of exercise capacity might also be useful for the early detection of parenchymal involvement and diagnosis of sarcoidosis-associated pulmonary hypertension. Both muscle weakness and exercise intolerance have been suggested as underlying causes of fatigue and dyspnea complaints, resulting in reduced QoL. Research is required to find out whether a multidisciplinary rehabilitation program is of clinical benefit in the management of sarcoidosis patients.

Summary

This review underlines the added value of physical testing in the management of sarcoidosis patients, especially in those with unexplained physical complaints.

Introduction

Sarcoidosis is a multisystem disorder of unknown origin, which is characterized by noncaseating epithelioid cell granulomas.[1-3] The course of sarcoidosis is unpredictable and clinical manifestations are variable, depending on the organs involved, disease activity and severity. Patients often suffer from a wide spectrum of organ-specific symptoms. In addition to the lungs (>90%), the lymphatic system and the eyes are often affected.[2,4] Patients may also consult their physician with nonspecific health complaints, such as exercise intolerance, muscle weakness and fatigue.[5**-10] These sarcoidosis-related symptoms may be disabling for patients. The presence of disabling symptoms is defined as having more than one symptom that substantially influences a patient's daily activities and quality of life (QoL), and that cannot be explained from the results of routine investigations including lung function tests or chest radiographs.[11] The influence of muscle weakness and exercise intolerance on QoL has not been studied extensively.

Several studies have demonstrated that exercise intolerance, muscle weakness, fatigue and dyspnea are frequent problems in sarcoidosis.[5**,6,9] Possible factors involved in the development of such physical impairments are sarcoid muscle involvement, corticosteroid-induced myopathy, decreased pulmonary function and inflammatory processes. Moreover, inactivation because of the disabling symptoms may cause physical deconditioning as well.[6,12] Nevertheless, the primary cause of the physical impairments remains unclear.

Fatigue is the most frequently reported symptom in sarcoidosis (prevalence 50-80%), and is a clear hallmark of the disease.[5**,10,13] The cause of fatigue remains unknown and is most probably multifactorial. Reported cofactors are corticosteroid therapy, small fiber neuropathy, mood disorders like depression, cognitive failure[14], stress and anxiety[15], inflammatory activity and altered sleep patterns.[16,17] Physical impairment has been suggested to be associated with fatigue.[6,10] Another frequently reported symptom in sarcoidosis is dyspnea. Although pulmonary symptoms are the most common reason for treatment in sarcoidosis, the impact of dyspnea in relation to physical parameters has not been studied extensively.[6,7,9,10]

Physicians treating patients with sarcoidosis generally rely on conventional tests at rest, including lung function tests and imaging methods, and on indicators of disease activity during the follow-up and evaluation of a therapeutic response.[3] However, several studies have reported that these tests are only weakly related to nonspecific health complaints, including muscle weakness and exercise intolerance.[5**,10,13,18*] A physical assessment may be helpful in the management of exercise-related symptoms in sarcoidosis, especially in patients with unexplained disabling symptoms, to guide appropriate treatment.[19*]

This review focuses on the prevalence, assessment and treatment of muscle weakness and exercise intolerance in sarcoidosis and the association between these and fatigue, dyspnea and QoL.

Selection of studies

A computerized literature search was performed from 1997 up to 2013 using the search terms sarcoidosis and muscle strength, exercise capacity, fatigue, dyspnea and QoL. PubMed, Cinahl, Embase and the Cochrane Library were searched. Titles of interest were further reviewed by abstract. Reference lists of relevant studies were hand-searched for additional studies.

Studies included in this review met the following criteria: their objectives were to describe muscle weakness and exercise intolerance in sarcoidosis; their study samples included sarcoidosis patients; the articles were full reports; the studies were published in English.

Assessment of muscle weakness

Although peripheral muscle weakness is a frequently reported symptom in sarcoidosis, the number of studies on this topic is limited.[5**-7,19*,20] Marcellis *et al.*[5**] found peripheral muscle weakness in sarcoidosis patients (n=124) compared with healthy controls. Handgrip force, elbow flexor muscle strength, isokinetic quadriceps and hamstrings peak torque were reduced in 12-27% of the population studied. Similarly, Spruit *et al.*[6] found reduced handgrip force and quadriceps strength in fatigued sarcoidosis patients compared with healthy controls.

In line with previous studies, a retrospective study by Marcellis *et al.*[19*] found reduced handgrip force in symptomatic sarcoidosis patients. Korenromp *et al.*[20] also found reduced peripheral muscle strength in patients with sarcoidosis in clinical remission.

Involvement of the diaphragm and intercostal muscles may result in respiratory muscle failure, and inspiratory (maximal inspiratory mouth pressure (PImax)) and expiratory (maximal expiratory mouth pressure (PEmax)) muscle weakness are indeed rather common in sarcoidosis.[7] Marcellis *et al.*[5**,19*] showed that PImax, assessed by measuring maximal respiratory mouth pressures, was reduced in more than 40% of the sarcoidosis patients studied. Several studies showed reduced mean respiratory endurance time, PImax and PEmax values in patients with sarcoidosis compared with healthy controls[6,8,21-23] and in fatigued compared with nonfatigued sarcoidosis patients in an acute phase of the disease and in clinical remission.[10,20] In contrast to Baydur *et al.*[22], Brancaleone *et al.*[23] did not find a correlation between PImax and lung function test results. Reduction of inspiratory muscle endurance has also been reported, even in patients with normal lung function test results, which may indicate inspiratory muscle fatigue.[8,23]

So far, only cross-sectional study designs have been used to assess the prevalence of muscle weakness and exercise intolerance in sarcoidosis. As a result, no conclusions

can be drawn with regard to disease progression. Recently, a 2-year follow-up study by Marcellis *et al.*[24] showed that these impairments had a persistent character.

Assessment of exercise intolerance

Maximal exercise testing (cardiopulmonary exercise testing (CPET)) and submaximal exercise testing (6-minute walk test (6MWT) and 6-minute stepper test (6MST)) appeared to be useful in detecting exercise limitations and deciphering exercise-related symptoms.[19*,25-27*]

CPET on a cycle ergometer or treadmill provides an overall measure of integrated exercise responses, which are not adequately reflected by measurements of individual organ system function.[26] Several studies reported reduced maximal oxygen uptake (VO_2max) in sarcoidosis patients, with a prevalence between 50% and 88%.[6,19*,23,28-30,31*,32] A reduction in VO_2max can be accounted for by muscle weakness, pulmonary and cardiovascular function impairments. Quadriceps peak torque was positively correlated with peak external work rates (r=0.47) assessed by a maximal incremental cycle exercise test. In addition, sarcoidosis patients reported higher Borg scores for leg fatigue after the peak exercise test.[6] A study by Miller *et al.*[33] also found that 67% of the sarcoidosis patients terminated their peak exercise test because of 'leg complaints', which was considered an indication of skeletal muscle weakness.

CPET is useful in the early detection of parenchymal involvements, including pulmonary gas exchange impairments (PGEI), in sarcoidosis patients with normal lung function test results and chest radiographs without signs of parenchymal involvement.[19*,34,35] Physical impairments such as PGEI, which are not yet recognizable at rest, often become apparent during exercise. In contrast to the resting situation, in which the apical regions of the lung contribute relatively little to ventilation and gas exchange, these regions normally contribute to meeting the increasing demands of ventilation and gas exchange during exercise. As sarcoidosis lesions favor the apical regions of the lung, CPET may be a sensitive tool to detect the presence and progression of parenchymal disease.[28,35] An abnormally increased alveolar–arterial oxygen pressure gradient at maximal exercise (P(A-a)O_2max) in sarcoidosis may reflect impairment of the gas exchange area, barrier thickness, ventilation-perfusion-diffusion mismatching of the lung or a decline in mixed venous partial oxygen pressure.[19*,28,31*,36]

Lopes *et al.*[31*] demonstrated that the outcome measures of CPET, P(A-a)O_2max and breathing reserve are predictors of a decline in pulmonary function in patients with rather severe thoracic sarcoidosis.

The 6MWT is a submaximal exercise test which is a widely used alternative to CPET to assess exercise and functional capacity. The test is easy to use, inexpensive, reproducible and more patient-friendly.[37,38] Marcellis *et al.*[5**] showed reduced 6-minute walking distance (6MWD) in 45% of a sample of sarcoidosis patients. In line with this, Kabitz *et al.*[21] also found reduced mean 6MWD in male patients and

Spruit *et al.*[6] found the same in fatigued sarcoidosis patients compared with healthy individuals. Alhamad[39] and Baughman *et al.*[40] found that 73% and 51% of their respective sarcoidosis samples had a 6MWD of less than 400 m. In addition to the 6MWD, the distance–saturation product (DSP), defined as the product of 6MWD and the lowest oxygen saturation during the 6MWT, as well as the Borg dyspnea score, may be useful indicators of functional status and QoL in patients with sarcoidosis.[18*,41] Integration of the 6MWT in the work-up of sarcoidosis patients may also be useful for the diagnosis of sarcoidosis-associated pulmonary hypertension.[38,40,41]

Lack of space can prevent the performance of a 6MWT. A study of patients with various diffuse interstitial lung diseases (ilds), including sarcoidosis, found that the 6MST appeared a suitable alternative to the 6MWT. The number of steps achieved in the 6MST was strongly correlated with the 6MWD.[27*] The sensitivity and reproducibility of this test were demonstrated for several patient groups, including ild.[42,43]

Relation of muscle weakness and exercise intolerance with fatigue, dyspnea and quality of life

Muscle weakness and exercise intolerance have been suggested as underlying causes of fatigue. Several studies reported that 6MWD, respiratory muscle weakness (PImax and PEmax) and peripheral muscle weakness (handgrip force and quadriceps peak torque) are positively related to fatigue.[6,8,20,40] Using a symptom inventory questionnaire, Drent *et al.*[10] showed that fatigued sarcoidosis patients are more likely to report exercise intolerance, muscle pain and dyspnea than nonfatigued patients. They also showed a more pronounced reduction in fat-free mass, as an expression of muscle wasting and loss of muscle bulk, in fatigued compared with nonfatigued patients. This may explain the reduced respiratory muscle strength in fatigued patients.[10] In contrast to previous studies, however, Marcellis *et al.*[5**] showed that fatigue was predicted neither by muscle strength nor by exercise capacity. Both fatigued and nonfatigued patients had to cope with these physical impairments. These studies underline the complexity of fatigue in sarcoidosis. Although the impact of muscle weakness and exercise intolerance on fatigue remains unclear, physicians should be aware that all patients might have these physical impairments.

Although the majority of patients with sarcoidosis have pulmonary manifestations, and although related symptoms are the most common reason for treatment, the impact of dyspnea on muscle strength and exercise capacity has not been studied extensively.[3] The Borg dyspnea scale has been applied to assess perceived dyspnea during exercise and is often administered before and after an exercise test.[44] Lung function test results did not correlate with the severity of perceived dyspnea measured with the British Medical Research Council scale.[22] However, reduced respiratory mouth pressures, in particular measured as twitch mouth pressure, were related to levels of dyspnea.[21,22] Thus, reduced respiratory muscle strength may affect the degree of

dyspnea.[21] Patients with inspiratory muscle weakness require greater utilization and effort of the available muscles to overcome an external workload during breathing. As a consequence, these patients may experience exertional dyspnea, resulting in reduced 6MWDs.[8,21] This underlines that respiratory muscle testing may provide additional information when the cause of dyspnea is unclear.[22] Several studies also showed that dyspnea may contribute to reduced 6MWD.[39-41] Hinz *et al.*[45*] found that dyspnea was an important symptom predicting anxiety and depression. Moreover, other comorbidities such as physical deconditioning, sleep apnea and pulmonary hypertension may also explain dyspnea sensations.[6,17,46]

QoL and health status are reduced in patients with sarcoidosis compared with healthy controls, and this reduction involves various clinical parameters.[6,47] General health status, measured by the King's Sarcoidosis Questionnaire, proved to be associated with forced vital capacity, sex, number of organs involved and immunosuppressant medication.[48*] Spruit *et al.*[6] showed that quadriceps peak torque was related to health status (with correlation coefficients of 0.44–0.70) as measured with the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). Marcellis *et al.*[5**] also showed reduced QoL in patients with peripheral muscle weakness. Brancaleone *et al.*[23] and Wirnsberger *et al.*[8] found a relation between respiratory muscle endurance and health status, although no such relationship was found between peripheral or inspiratory muscle strength and health status. The 6MWD proved to be associated with QoL and may serve as a potential target for interventions to improve QoL.[18*,40] Unlike exercise intolerance, fatigue appeared to be the most important predictor of QoL. In terms of improving patients' QoL, it has therefore been recommended to focus not only on objective but also on subjective health parameters.[9]

Treatment options

Too few intervention studies have examined the contribution of pharmaceutical treatment to the reduction of fatigue and exercise intolerance in sarcoidosis patients. Successful treatment of active sarcoidosis frequently fails to eradicate the disabling symptoms of persistent fatigue. This persistent malady, sarcoidosis-associated fatigue and exercise limitations may require nontargeted generalized fatigue strategies. To date, the most frequently employed pharmacologic strategies for fatigue have focused on the use of neurostimulants, neurostimulant-like drugs and tumor necrosis factor-α inhibitors.[16] Recently, Heij *et al.*[49] demonstrated that ARA reduced symptoms related to small fiber neuropathy, including fatigue and pain. They also found a significant improvement from baseline in the pain and physical functioning dimensions of the SF-36 QoL questionnaire. In addition to pharmaceutical treatments, rehabilitation and cognitive behavioral therapy should also be considered as treatment strategies.[16]

The development of physical impairments may involve physical deconditioning. For instance, patients suffering from fatigue, muscle weakness, exercise intolerance,

anxiety or depression may reduce their daily physical activities, resulting in general deconditioning. In turn, this may cause more perceived fatigue, exercise intolerance, muscle weakness and a further reduction in daily activities. This is called the negative vicious circle of physical deconditioning (Figure 2.1).[6,12,50]

Exercise training could be considered for those patients with persistent or progressive physical complaints. Huppmann *et al.*[51] demonstrated that pulmonary rehabilitation had a positive impact on the functional status of patients with ild, including their 6MWD, and on their QoL. Several studies have found exercise training to be effective in treating exercise intolerance, muscle weakness, fatigue and dyspnea and to improve QoL in chronic pulmonary diseases.[52-55] Although physical impairments are frequently mentioned symptoms of sarcoidosis and exercise training could be beneficial in reducing symptoms, the effects of exercise training have never been studied in a representative sarcoidosis population.

Additionally, cognitive therapy can be offered to patients with physical deconditioning because of psychological problems, such as anxiety and depression, to treat coping problems or stress perception with psychosocial counseling.[56] Patients may also benefit from other therapeutic options, such as dietary interventions and supplemental oxygen.[12]

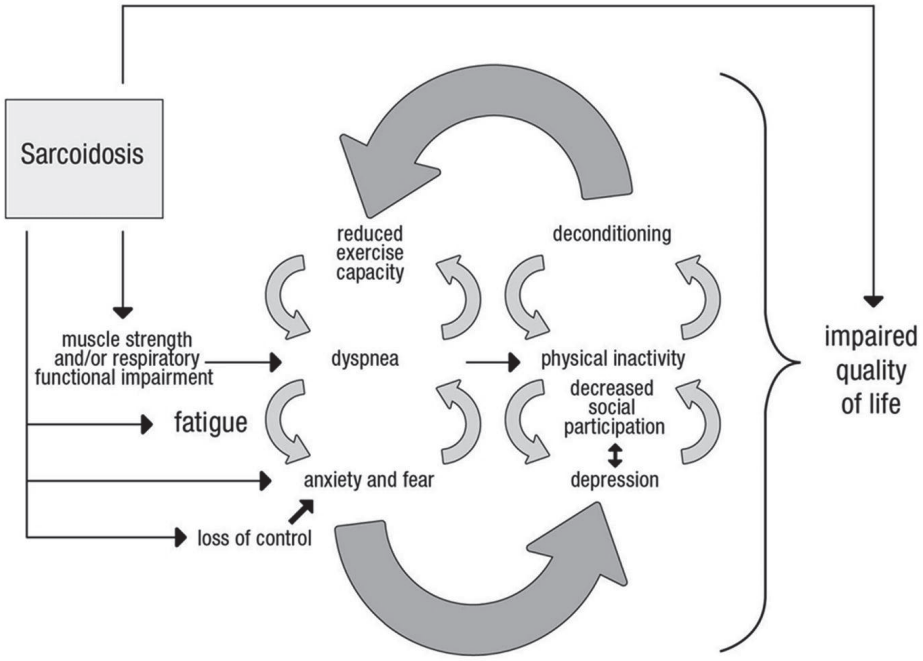

Figure 2.1 Negative vicious circle of physical deconditioning: disabling symptoms in sarcoidosis can reduce daily physical activities, resulting in general deconditioning and a reduced quality of life (adapted from[50]).

Clinical implications

The nature of sarcoidosis underlines the need for a multidisciplinary approach. As the management of sarcoidosis has not been standardized, guidelines and recommendations are essential to further optimize the management of these patients. In clinical practice, routinely performed tests during the evaluation and follow-up of sarcoidosis include laboratory and pulmonary function testing at rest and chest radiographic imaging. However, these tests appear to be unreliable predictors of exercise capacity, functional capacity and health status. As this review has highlighted, muscle weakness and exercise intolerance appear to be a substantial problem in sarcoidosis, so we recommend the inclusion of tests to assess muscle strength and exercise capacity in the management of sarcoidosis (Table 2.1). In addition to a 6MWT and/or peripheral muscle weakness, respiratory muscle strength testing should be considered for patients with dyspnea complaints, by measuring maximal respiratory mouth pressures. Additionally, patients should complete the Fatigue Assessment Scale and a dyspnea scale. These tests are inexpensive and easy to perform. If the cause of exercise-related symptoms still remains unclear, a CPET with blood gas analyses could be useful.

Table 2.1 Recommended muscle strength and exercise tests to be included in the regular work-up of sarcoidosis patients.

	Physical test	Optional
Muscle strength		
Upper extremity	Musculus biceps (hand-held dynamometer) or Handgrip strength (Jamar dynamometer)	
Lower extremity	Musculus quadriceps (hand-held dynamometer)	Biodex
Respiratory	Respiratory mouth pressures (pressure transducer)	
Exercise capacity		
Submaximal	6-minute walk test	
Maximal		Cardiopulmonary exercise testing with blood gas analysis (for patients with unexplained exercise-related symptoms)

Conclusion

Muscle weakness and exercise intolerance are frequent problems in sarcoidosis, with a persistent character. More research is needed to standardize the assessment of these symptoms. This review underlines the value of physical testing in the screening and follow-up of sarcoidosis patients, especially those patients with unexplained physical complaints. We therefore recommend including physical testing in the multidisciplinary management of sarcoidosis. Although the impact of muscle weakness and exercise

intolerance on fatigue and dyspnea remains unclear, physicians should be aware that fatigued and dyspneic patients can also have these physical impairments, resulting in reduced QoL. Although exercise training has proved beneficial in several chronic diseases, research as to whether a multidisciplinary rehabilitation program would be of clinical benefit in the management of sarcoidosis patients is urgently needed.

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