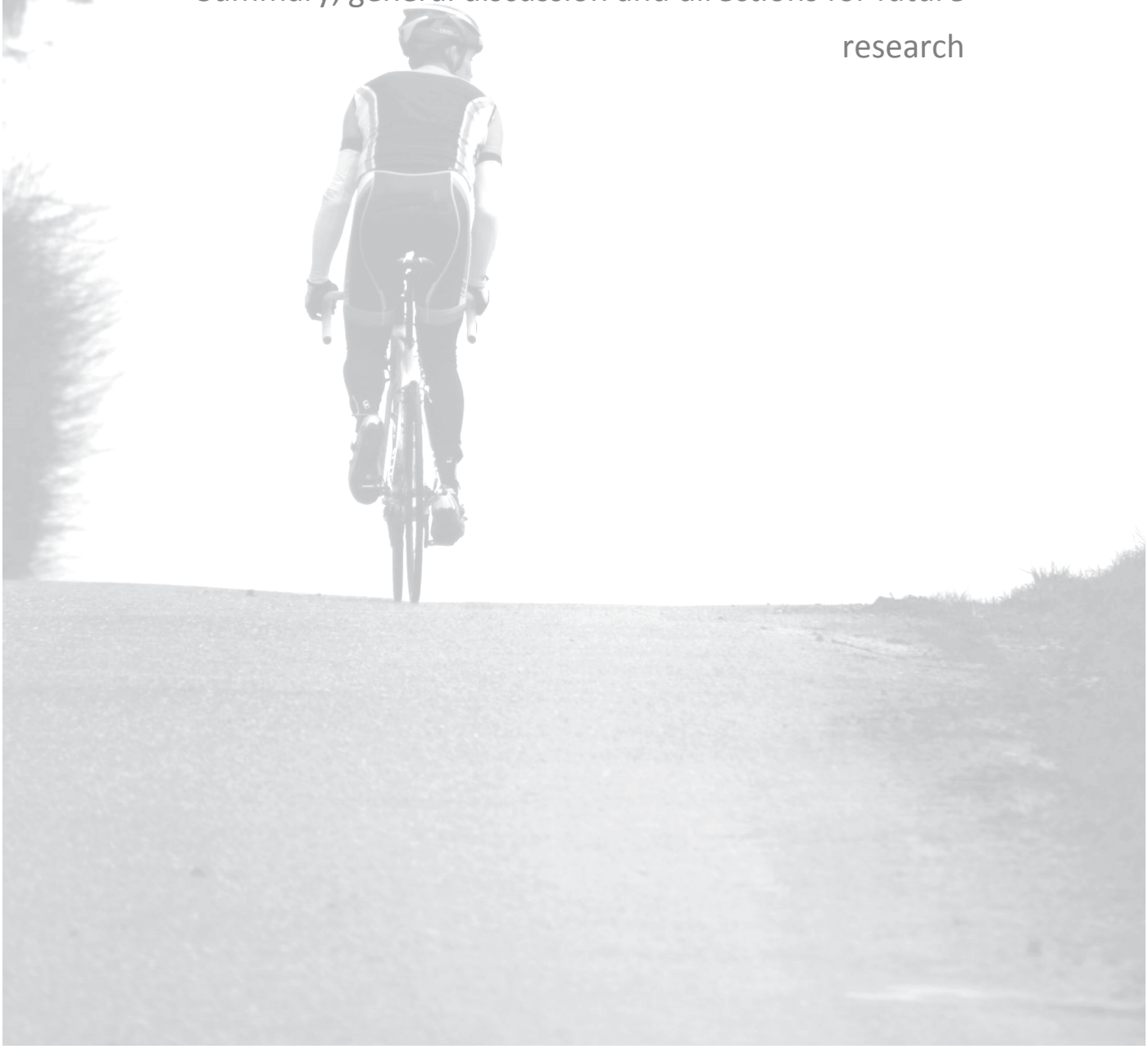
Chapter 8

Summary, general discussion and directions for future research



Summary

The clinical presentation and course of sarcoidosis are highly variable, depending on various disease and patient characteristics.[1] Besides respiratory and other organ-specific problems, sarcoidosis patients frequently suffer from systemic symptoms, like general weakness, exercise intolerance, and fatigue.[1,2] These sarcoidosis-related disabling symptoms can significantly reduce a patient's quality of life (QoL).[3] Generally used medical assessments, including lung function tests or chest radiographs, often appear inappropriate to explain the physical impairments, and correlate weakly with QoL.[3-5] Nevertheless, appropriate physical assessment is important in the management of sarcoidosis, to monitor the disease burden and the course of the disease, and possibly to guide therapeutic interventions. Understanding the associations between physical impairments and both subjective and clinical variables is essential to identify patients' needs. Physical testing can be helpful in assessing physical limitations due to sarcoidosis, in order to improve patient-centered care. However, standardized management strategies for the assessment and treatment of physical impairments in sarcoidosis are lacking. Although physical training of patients with chronic respiratory diseases has proven to be beneficial in improving physical functions and QoL, scientific evidence on the impact of training in sarcoidosis is scarce.[6,7]

The aims of the studies presented in this thesis were to assess whether patients with sarcoidosis suffer from physical impairments, and to determine the value of physical testing in the management of sarcoidosis. To this end, we measured the prevalence of muscle weakness, exercise intolerance, and fatigue among patients with sarcoidosis. In addition, we evaluated the predictive value of physical functions for fatigue and QoL. These studies included patients with sarcoidosis who were referred to the former ild (interstitial lung diseases) care team of the Maastricht University Medical Centre, a tertiary care center in the Netherlands. Finally, the impact of physical training on physical functions and QoL in sarcoidosis was studied in a pilot study with a single-group pre-post measurement design, among sarcoidosis patients referred for physical therapy by their pulmonologist at the Orbis Medical Center in the Netherlands.

Overview of main findings

Chapter 1, the general introduction, presents a summary of the pathogenesis, epidemiology, clinical features, and course of sarcoidosis. It also discusses the possible role of physical assessment and exercise training in the management of sarcoidosis and presents an outline of the thesis.

Chapter 2 provides an overview of the literature concerning the prevalence, assessment, and treatment of muscle weakness and exercise intolerance in sarcoidosis patients and the associations between these physical impairments and fatigue, dyspnea, and QoL. Muscle weakness and exercise intolerance appear to be frequent problems in sarcoidosis, with a persistent character. The results of routinely performed clinical tests, such as lung function tests and imaging methods, correlate only weakly

with these nonspecific physical health complaints. Exercise testing can be used to identify the presence of strength deficits and exercise intolerance. Assessment of exercise capacity might also be useful for the early detection of parenchymal involvement and the diagnosis of sarcoidosis-associated pulmonary hypertension. Both muscle weakness and exercise intolerance have been suggested as underlying causes of fatigue and dyspnea complaints. Hence, physicians should be aware that fatigued and dyspneic patients may have physical impairments, resulting in reduced QoL. This chapter underlines the clinical relevance of physical testing in sarcoidosis patients, especially those with unexplained physical complaints. Although exercise training has proved beneficial in several chronic pulmonary diseases, the effects of exercise training have hardly been studied in a representative sarcoidosis population. Research as to whether a multidisciplinary rehabilitation program is of clinical benefit in the management of sarcoidosis patients is urgently required.

Chapter 3 reports on the prevalence of exercise intolerance, muscle weakness, and fatigue in 124 sarcoidosis patients and the predictive value for fatigue of exercise capacity, muscle strength, and other demographic (sex, age, body mass index, fat-free mass, and time since diagnosis) and clinical (lung function tests, radiographic staging, prednisone use, and inflammatory markers) characteristics. Patients performed a six-minute walk test (6MWT), and their handgrip force (HGF), elbow flexor muscle strength (EFMS), quadriceps (QPT), and hamstring peak torque (HPT) were measured. Maximal inspiratory pressure (PImax) was recorded and all patients completed the Fatigue Assessment Scale (FAS). The data of 62 healthy controls were used as a reference for the physical test results. The 6MWT was found to be reduced in 45% of the population, while HGF, EFMS, QPT, and HPT muscle strength were reduced in 15%, 12%, 27%, and 18%, respectively. PImax was reduced in 43% of the population, and 81% of the patients reported fatigue. Exercise intolerance and muscle weakness occurred in both fatigued and nonfatigued patients. Patients with reduced peripheral muscle strength of the upper and/or lower extremities were more fatigued and had impaired lung functions, fat-free mass, PImax, 6MWT, and QoL compared to patients without muscle strength impairment. However, according to a multiple regression analysis, fatigue was predicted neither by exercise capacity nor by muscle strength. The results demonstrate that fatigue, exercise intolerance, and muscle weakness are frequent problems in sarcoidosis. Physical tests should be conducted in the multidisciplinary management of sarcoidosis patients, even in nonfatigued patients. More research is needed to standardize the assessment of physical impairments in sarcoidosis.

Chapter 4 presents the changes in the prevalence of exercise capacity, muscle weakness, and fatigue, and the changes in these parameters in individual sarcoidosis patients during a 2-year follow-up study. All participants of the 2008/9 study (chapter 3) living in the southern part of the Netherlands (n=104) were invited to participate in the follow-up measurement. Fourteen of these patients were unable to participate. In the end, 90 sarcoidosis patients of the 2008/9 study participated in this 2-year follow-up

study. At follow-up, patients performed the physical tests and completed the questionnaires mentioned in chapter 3. Both at baseline and follow-up, a substantial proportion of the patients showed a reduced 6MWT (41.6% and 34.8%, respectively), EFMS (6.7% and 14.6%), QPT (21.3% and 18.0%), HPT (13.5% and 12.4%), and PImax (45.9% and 48.6%). The majority of the patients reported fatigue (86% and 77%). These physical impairments had remained stable during the follow-up period. The literature reports that nearly two-thirds of sarcoidosis patients may show spontaneous remission in the first two years after diagnosis, while sarcoidosis becomes chronic (>2 years) or progressive in 10-30%. However, the prevalence of physical impairments among patients diagnosed with sarcoidosis less than two years before inclusion in this study was similar to that among patients with a longer history of the disease. This study highlights that exercise intolerance, muscle weakness, and fatigue are frequent problems in symptomatic sarcoidosis patients, with a stable and persistent character.

Chapter 5 describes the added value of cardiopulmonary exercise testing (CPET) with blood gas analysis on a bicycle ergometer compared to the measurement of the diffusing capacity of the lung for carbon monoxide at rest (DLCO) in detecting impaired pulmonary gas exchange, based on a study in 160 symptomatic sarcoidosis patients. Of the patients with normal DLCO (n=99, 61.9%), the alveolar-arterial oxygen pressure difference ($P(A\text{-}a)O_2$) at maximal exercise was moderately increased (>2.5 kPa) in 69.7% and excessively increased (>4.7 kPa) in 18.2%. Pulmonary gas exchange impairment (PGEI) was more obvious in patients with lower DLCO values. A DLCO value below 60% of predicted indicated substantial gas exchange impairment. Arterial oxygen pressure at rest, DLCO, and forced vital capacity as a percentage of predicted and radiographic staging predicted 40% of the PGEI at maximal exercise. We concluded that normal DLCO did not rule out abnormalities in pulmonary gas exchange at maximal exercise, suggesting that normal DLCO at rest is an inappropriate predictor of abnormal pulmonary gas exchange during exercise. CPET appeared to offer added value in detecting impaired gas exchange during exercise in sarcoidosis patients with unexplained disabling symptoms.

Chapter 6 assesses the associations between QoL and physical functions in sarcoidosis and evaluates whether these associations change over a 2-year period. Since two patients of the population reported on in chapter 4 did not complete the World Health Organization Quality of Life assessment instrument (WHOQOL-BREF), 88 sarcoidosis patients participated in this study. At baseline and follow-up, patients performed the physical tests discussed in chapter 3. Besides physical tests, patients completed the WHOQOL-BREF and the FAS. QoL of the sarcoidosis patients remained stable over a 2-year course of the disease, and was reduced compared with healthy controls, particularly regarding the physical health domain. Both at baseline and follow-up, fatigue and the six-minute walking distance showed strong associations with QoL. Fatigue and exercise capacity predicted the scores for the WHOQOL-BREF physical health domain at baseline (59%) and follow-up (64%). QoL at baseline was the best predictor of QoL at follow-up. Since fatigue and exercise capacity showed important

stable associations with QoL, these measurements should therefore be included in the management of sarcoidosis. Future studies should investigate whether exercise training might be useful to treat physical impairments and improve QoL.

Whereas pulmonary rehabilitation has become standard care for patients with chronic obstructive pulmonary disease, scientific studies on the benefits of physical training in sarcoidosis are scarce. **Chapter 7** shows the results of a pilot study examining the impact of a 13-week physical training program on fatigue, physical functions, and QoL in 18 fatigued sarcoidosis patients and/or patients with exercise intolerance. The FAS, WHOQOL-BREF, Medical Research Council (MRC) dyspnea scale, Visual Analogue Scale (VAS), 6MWT, submaximal bicycle test and muscle strength of the quadriceps and elbow flexors were assessed at baseline and after the program. This pilot study found that FAS scores had decreased (mean difference -2.7 points, 95% CI -4.4 to -1.1) after completion of the training program, along with improvements in the WHOQOL-BREF psychological health domain (mean difference 0.9 points, 95% CI 0.2 to 1.7) and MRC dyspnea score (mean difference -0.4 points, 95% CI -0.8 to -0.1). 6MWD improved by 34.6 m (95% CI 20.3 to 49.0) and mean heart rate on the bicycle test also improved (mean difference 8.4 beats/minute, 95% CI -13.8 to -3.0), as did quadriceps strength (mean difference 10.7 kg, 95% CI 5.5 to 15.9). No changes were observed in VAS score or elbow flexor muscle strength. Although the training effects were small, we concluded that fatigue seems to be reduced and both psychological health and physical functions seem to improve after a period of physical training for sarcoidosis patients. Future studies are warranted to assess the benefits of physical training in sarcoidosis.

Highlights of this thesis

In conclusion, this thesis presents several aspects of ways to optimize the assessment and treatment of physical impairments in sarcoidosis. Exercise intolerance, muscle weakness, and fatigue are shown to be frequent problems in symptomatic sarcoidosis patients, with a stable and persistent character. Exercise intolerance and muscle weakness occur in both fatigued and nonfatigued patients. CPET appears to offer added value in detecting impaired pulmonary gas exchange during exercise in sarcoidosis patients with unexplained disabling symptoms and with a normal DLCO and spirometry and chest radiography not showing parenchymal involvement. These findings indicate the importance of including physical testing in the multidisciplinary management of sarcoidosis, even in nonfatigued patients. Fatigue is predicted neither by physical nor by clinical parameters. We therefore recommend including a measure of fatigue in the follow-up of sarcoidosis patients. QoL is an important aspect of patient-centered care, and measurements of QoL are considered to be major therapeutic outcome measures. Since QoL is an abstraction, a key to improving it lies in understanding the association between QoL and functional impairments. Sarcoidosis has a major impact on patients' lives, and often reduces QoL. Fatigue and exercise capacity show important stable associations with QoL, suggesting that these physical parameters are important intervention targets to indirectly improve QoL. Finally, fatigue, psychological health and

physical functions tend to improve after a period of physical training in sarcoidosis patients. However, future studies are warranted to assess the benefits of physical training in sarcoidosis.

General discussion

The population of sarcoidosis patients is a heterogeneous group, characterized by a broad range of specific and non-specific health complaints, depending on the organs involved. In addition to reporting primary complaints like shortness of breath due to pulmonary dysfunction, these patients often visit their physician with subjective physical health complaints, including muscle weakness and exercise intolerance. Although evidence regarding the effectiveness of physical training in sarcoidosis is scarce and generally of low quality, physicians do refer their patients with physical health complaints to physical therapy.

In line with evidence-based practice, scientific evidence in this field is necessary to support this treatment option. Research could start by examining whether physical complaints are secondary complaints in sarcoidosis patients in general. When we started our research project, the literature did not unequivocally show that sarcoidosis patients do suffer from physical impairments.[8,9] In a case-control study, we found high prevalence rates of physical impairments in these patients (chapter 3). It is well-known that many sarcoidosis-related disabling symptoms are self-limiting in a few years.[1] Knowing the natural course of a disease or symptoms is a key factor in the critical appraisal of therapeutic effectiveness/efficacy. The persistent character of physical impairments in sarcoidosis was objectively examined in a longitudinal study (chapter 4). To objectify physical impairments, valid and reliable test procedures are essential. Cardiopulmonary exercise testing appeared beneficial in detecting impaired pulmonary gas exchange during exercise in sarcoidosis patients with unexplained disabling symptoms (chapter 5). These studies show the importance of physical testing in the management of sarcoidosis to define disease phenotypes and burden, and to assess disease progression. Unfortunately, no standardized procedure to establish the presence of physical impairments in sarcoidosis is available.

Exercise training is a generally accepted treatment strategy in chronic lung diseases to reduce physical impairments. Our interventional pilot study (chapter 7) showed that physical training seemed feasible and safe in sarcoidosis patients. However, the training effects were small in terms of fatigue reduction and improvements of QoL and physical functions. The final chapter critically discusses the main findings and implications presented in this thesis.

The review study

The review presented in chapter 2 underlines the added value of physical testing in the management of sarcoidosis patients. Although this was a narrative review, we included

as many as possible of the features of a systematic review. In general, a review is a cost-effective and efficient way to evaluate the available evidence on a particular topic, and provides health care professionals with an easy-to-read and up-to-date overview and summary of recent advances. A systematic review is based on a clearly formulated question, identifying relevant studies and assessing their quality, summarizing the evidence by methodological means, and finally interpreting the findings.[10] Although the research question in our review was clearly formulated, a systematic review requires a more specific research question which is generally limited to one topic.[10] Although an extensive computerized literature search was performed using various electronic libraries, and reference lists of relevant studies were hand-searched, this was done by only one author. Inclusion criteria were reported. Included studies were limited to those published in English, probably resulting in some selection bias. Despite a thorough literature search, we found only a limited number of studies in this field, so we chose to include studies regardless of the quality of their design, whereas a quality assessment is normally required to explore the heterogeneity of studies and determine whether a meta-analysis is suitable.[10] Since our review thus has some qualitative limitations compared to a systematic review, the recommendations must be interpreted with caution. Finally, it is not common in a systematic review to give a subjective opinion about the topic, as we did.

Prevalence and course of physical impairments in sarcoidosis

As in other chronic diseases, muscle weakness and exercise intolerance were shown to be frequent problems in sarcoidosis, with a stable and persistent character (chapters 3 and 4).[11,12] These physical impairments occur in both fatigued and nonfatigued patients.

In sarcoidosis, muscle strength of the quadriceps is related to exercise capacity.[8] Just as in chronic obstructive pulmonary disease (COPD), peripheral and respiratory muscle weakness contributes to exercise limitations, and lower limb muscles are most often involved.[13] Involvement of the upper limb muscles in daily activities may cause relative preservation of these muscles.[12]

These case-control studies included refractory sarcoidosis patients referred to a tertiary referral center. One could argue that these patients generally suffer from more severe physical health complaints than patients visiting secondary health care services, which may have caused selection bias, affecting the generalizability of these results. However, the studies included patients in all stages of the disease.

Our longitudinal study used a follow-up period of two years. Over such a period, many things in a patient's life may change. For example, substantial life events (change of job, becoming a parent or health problems other than sarcoidosis) or a change in pharmaceutical or non-pharmaceutical treatment strategies can influence study results. Remembering these events over the past two years can be very difficult and may result in loss of relevant details. Signaling these changes on a frequent basis is important for a better understanding of the course of a disease or physical impairments. A prospective assessment of life events and interventions is preferable, for example using a diary.

During the follow-up period, several assessors participated in this study, which might have caused problems in terms of inter-rater reliability. To solve this problem as much as possible, assessors were trained to perform the measurements in an identical way.

Physical assessment

This thesis recommends incorporating physical assessment in the follow-up of sarcoidosis patients (Table 2.1; chapter 2). To date, however, no standardized physical assessment set is available.

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)

A retrospective cohort study (chapter 5) showed the added value of cardiopulmonary exercise testing in the follow-up of sarcoidosis patients with unexplained disabling symptoms. Such a retrospective study design has both advantages and disadvantages. Compared to a prospective cohort study, a retrospective study is inexpensive and quick to carry out, since existing data are used for the analyses. Our study analyzed the data from a clinical database. An important disadvantage of this design is that the investigator depends on the availability and accuracy of the clinical records.[14] Although the test procedures for the cardiopulmonary exercise test and lung function tests were specified in a protocol, it always remains questionable for the investigator whether the tests were performed in an identical way.

The Biodex System 3 Pro dynamometer (Biodex Medical Systems, Shirley, New York, USA), which is the gold standard in muscle strength testing, was used to assess muscle weakness of the quadriceps in sarcoidosis. However, this system is quite expensive and not portable, resulting in practical limitations for its daily use. The microFET (Biometrics, Almere, the Netherlands), a hand-held dynamometer, could offer a reliable alternative to measure peripheral muscle strength.[15] Inspiratory mouth pressure was measured at the Department of Respiratory Medicine of the hospital by

trained employees. Nowadays, reliable, easy-to-use and portable devices are available to measure respiratory mouth pressures.[16] The six-minute walk test (6MWT) is a frequently used exercise test in sarcoidosis. According to the American Thoracic Society this test requires a straight line walking course of 30 m, so lack of space can restrict the use of this test.[17] The 6MWT over a 10 m walking course is a suitable alternative, since Beekman *et al.*[18] recently published reference equations for this test. A six-minute stepper test has also been suggested as an alternative, since the number of steps strongly correlates with the six-minute walking distance.[19] CPET with blood gas analysis may be helpful, especially when there is a discrepancy between clinical findings and physiological tests at rest (chapter 5). Although CPET is the gold standard in exercise testing, it is often not a first-choice measurement. This measurement is expensive, time-consuming, requires complex equipment and involves highly trained staff. The modified shuttle walk (MSWT) test and 6MWT may be good alternatives, since CPET results show good correlations with those of the MSWT and 6MWT.[20,21]

The physical tests mentioned in the above section are all volitional tests, so their results partially depend on patients' motivation and cooperation during the test. Nonvolitional testing would probably yield more valid results. For example, repetitive magnetic stimulation of the femoral nerve can be used to induce and quantify quadriceps endurance.[22,23] In general, however, sarcoidosis patients are very cooperative and motivated to participate in research projects.

Training program

A pilot study was conducted to examine the changes in fatigue, QoL, and physical functions in sarcoidosis patients following a 13-week physical training program (chapter 7). Scientific evidence regarding the trainability of sarcoidosis patients and the effectiveness of training programs in sarcoidosis is scarce.[6,7] Since the potential study population in the Sittard-Geleen region of the Netherlands was limited, an uncontrolled interventional pilot study was chosen to examine the potential benefits of physical training in sarcoidosis.

Unfortunately, this study was underpowered, since the number of patients it included was smaller than had been indicated by the sample size calculation. Hence its results should be interpreted with caution.

Since the pilot study did not include a control group, it could not show the effectiveness of physical training in reducing physical impairments in sarcoidosis compared with no treatment or usual care.

In line with Strookappe *et al.*[7], physical functions in our sarcoidosis patients seemed to improve following a 13-week physical training program designed for sarcoidosis patients (chapter 7), although the improvements were smaller than in their study. Some factors may have contributed to the smaller improvement. One could argue that higher intensity training, as advocated in international guidelines[24,25], might have yielded greater impact. However, sarcoidosis patients often suffer from severe physical impairments, like arthralgia and muscle pain, and a high-intensity training

program may worsen these complaints, resulting in high dropout rates. Therefore, we deliberately opted for a low- to moderate-intensity training program in this study. However, this intensity may be insufficient to induce a physiological adaptation of the cardiovascular and musculoskeletal system.[26]

The frequency and duration of the training program were in line with international guidelines[24,25], so these training parameters would seem to be sufficient. Physical training might also cause increased levels of inflammatory markers and cytokines, explaining sarcoidosis-associated symptoms.[27,28] A training frequency of three times a week could affect the recovery period. Although Braam *et al*.[28] showed higher levels of biochemical parameters in sarcoidosis patients compared to healthy controls before an exercise test, changes in these levels in response to exercise were similar in both groups. Hence, the biochemical response during exercise and the recuperative capacity after maximal exertion by sarcoidosis patients appear similar to those of healthy controls.

The physical training included peripheral muscle strength and endurance training. Since respiratory muscle weakness is also common in sarcoidosis, respiratory muscle training could be a valuable addition to general exercise training in sarcoidosis, especially for those with respiratory limitations during exercise.[26] The additional benefits of multidisciplinary pulmonary rehabilitation (PR) should also be studied. Besides physical training, multidisciplinary PR includes education and behavior change to improve the physical and psychological condition of people with chronic respiratory disease and to promote disease management.[26]

Cause of physical impairments

The studies presented in this thesis show that physical impairments do occur in sarcoidosis. However, the primary cause of these impairments remains unknown. Several factors may contribute to the development of physical impairments. Exposure of a genetically predisposed person to antigens may cause an inflammatory response with granuloma formation in sarcoidosis. The most important characteristic of sarcoidosis is systemic inflammation with increased levels of cytokines and chemokines, such as tumor necrosis factor-alpha (TNF-α) and interleukins (Figure 8.1).[28-30] It is assumed that these inflammatory markers initiate protein breakdown in skeletal muscles.[5,31] In addition, systemic inflammation can be a trigger for oxidative stress, which may contribute to muscle dysfunction in chronic diseases.[32,33] The exaggerated immune response also causes granulomas in sarcoidosis. Sarcoid muscle involvement is commonly demonstrated, although it is mostly asymptomatic.[34] Recently, Cremers *et al.*[35] showed that ^{18}F-FDG-PET/CT was useful in detecting muscle involvement in sarcoidosis. Unfortunately, it remains unclear whether sarcoid muscle involvement is related to muscle weakness. In addition, corticosteroid-induced myopathy is a well-known side-effect of corticosteroid treatment in sarcoidosis.

Another substantial problem in sarcoidosis appears to be muscle atrophy.[36] Our sarcoidosis patients with reduced peripheral muscle strength demonstrated impaired

lung functions and reduced fat-free mass (FFM) (chapter 3), which may be an expression of muscle wasting. Therefore, loss of muscle bulk might be a determinant of muscle strength. Unfortunately, muscle mass was not directly measured in our study. A recent study by Cremers *et al.*[36] showed conflicting results. They found normal muscle strength but reduced exercise capacity in muscle atrophic patients compared to patients with normal muscle mass. Finally, physical inactivity caused by perceived disabling symptoms, like lung function impairments, fatigue, dyspnea, cognitive failure, and depression, can induce physical deconditioning, resulting in more perceived fatigue and physical inactivity. In the long term, this negative circle of deconditioning may cause exercise intolerance and muscle weakness.[37] Unfortunately, generally used medical assessments cannot distinguish between these different causes, so future studies are necessary to demonstrate the primary cause of the physical impairments. Although knowledge about the etiology of physical impairments is essential to guide treatment strategies, this was beyond the scope of this thesis.

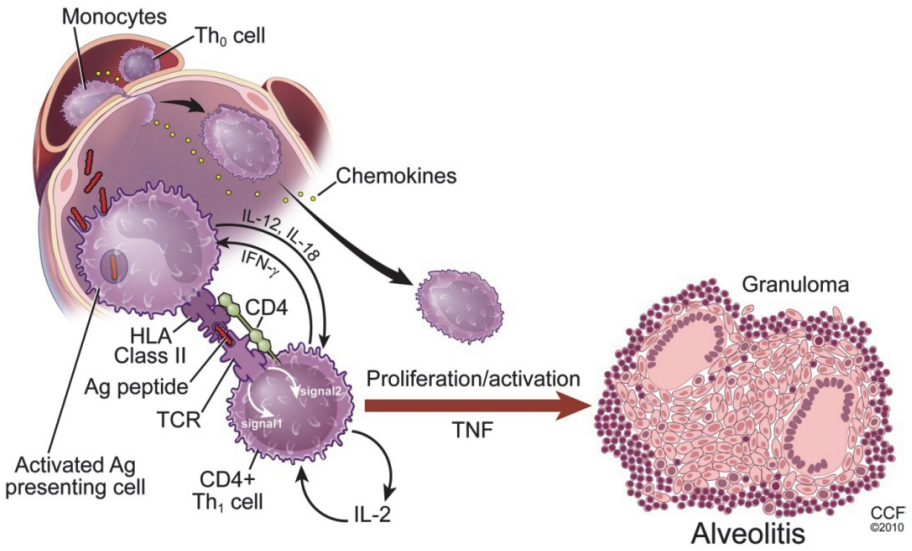


Figure 8.1 Schematic presentation of the inflammatory response with granuloma formation in sarcoidosis. An antigen induces antigen-specific Th1-mediated granulomatous inflammation with production of Th1 cytokines (IFN-γ, IL-2). Granuloma formation is set in motion by activated macrophages and T-cells, along with other effector cells (e.g. fibroblasts) under the regulatory influence of local cytokine production. Removal of the antigen allows downregulation of the immune response. Alveolar macrophages activated in the context of a predominant Th2 response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis.[38] Ag, antigen; HLA, human leukocyte antigen; IFN- γ, interferon gamma; IL, interleukin; TCR, T-cell receptor; Th, T-helper; TNF, tumor necrosis factor. Adapted from Baughman et al.[30]

Practical implications

Since physical impairments are frequent problems in sarcoidosis, we recommend the use of physical tests in the diagnosis and evaluation of sarcoidosis patients, even in nonfatigued patients. Physical assessment should include submaximal exercise and peripheral muscle strength testing of the lower limbs and inspiratory muscle strength testing. In those patients with unexplained disabling symptoms, cardiopulmonary exercise testing can offer added value in detecting impaired gas exchange during exercise. Fatigue complaints cannot be predicted by physical or clinical test results. Therefore, a fatigue measure should also be included in the management of sarcoidosis. Although more research is necessary to assess the benefits of physical training in sarcoidosis, physical training might be considered in patients with physical complaints, to improve fatigue, physical functions, and QoL.

Directions for future research

Future research should focus on optimization of the physical assessment in sarcoidosis and the treatment options for physical impairments. This is necessary to avoid unnecessary exposure of patients to various clinical measurements and medical treatments because of inadequate management strategies.

Although it is clear that sarcoidosis patients frequently suffer from exercise intolerance and muscle weakness, the primary cause of these physical impairments remains unknown. As mentioned above, various hypotheses exist to explain the development of these impairments. A multidisciplinary research approach is necessary to identify the primary cause.

The study results presented in this thesis are a first step in the assessment of physical impairments in sarcoidosis. However, no standardized physical assessment battery is as yet available, so future studies should focus on the standardization and optimization of the physical assessment in sarcoidosis, incorporating the qualitative aspects, practical use, and costs of the measurements.

The Fatigue Assessment Scale (FAS) is a frequently used subjective fatigue measure in sarcoidosis with good psychometric properties.[39] Unfortunately, the FAS does not include an activity monitor, such as an accelerometer or activity questionnaire. Hence, patients may experience stable fatigue complaints even though their activity level has improved, resulting in an underestimation of their physical activity level. Optimal patient monitoring requires knowledge of their activity level in relation to fatigue complaints.

The minimal clinically important difference (MCID) is the smallest change score on an outcome measure across time which patients perceive as relevant.[40] This value is relevant for a clinician to interpret the clinical meaning of changes in outcome measures during the follow-up of individual sarcoidosis patients, since a statistically significant difference in outcome measure over time does not mean that this difference is relevant from the patients' point of view. An MCID value has been established for the

FAS,[40,41] but not for other measures frequently used in sarcoidosis, like the WHOQOL-BREF and 6MWT. Prospective cohort studies are needed to establish the MCID for primary outcome measures used in the management of sarcoidosis.

This thesis has reported short-term changes in fatigue, psychological health, and physical functions following a low-intensity physical training program in a small population of sarcoidosis patients. Although this pilot study provided some important evidence with regard to physical training in sarcoidosis, further research is required. Both the short- and long-term benefits of a physical training program in a larger sarcoidosis population should be studied, preferably using a randomized controlled trial design. Another point of debate concerns the intensity of the training. At the same time, the additional benefits of a multidisciplinary pulmonary rehabilitation program in sarcoidosis and the use of ambulatory oxygen during training in patients with pulmonary impairments should be studied.

Besides participation in a physical training program, telephone- or internet-based health (telehealth) coaching services can support sarcoidosis patients in monitoring their health, enhanceing self-management of their disease, and promoting an active lifestyle. A review by Dennis *et al.*[42] showed that telephone coaching is effective in chronically ill patients, including COPD patients, to improve health behavior, self-efficacy, and health status. It was especially in vulnerable patients or patients with limited access to health care that this service proved to offer added value in promoting better disease management. Tabak *et al.*[43] also showed that telehealth is effective in promoting better disease management and that patients' satisfaction with the program is good. Since studies of the effectiveness of telehealth in the management of sarcoidosis are lacking, prospective randomized controlled trials are necessary to examine whether telehealth programs are effective and provide added value in the management of sarcoidosis, and what kind of telehealth service would be most effective.

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