On the road to better care for patients with systemic sclerosis

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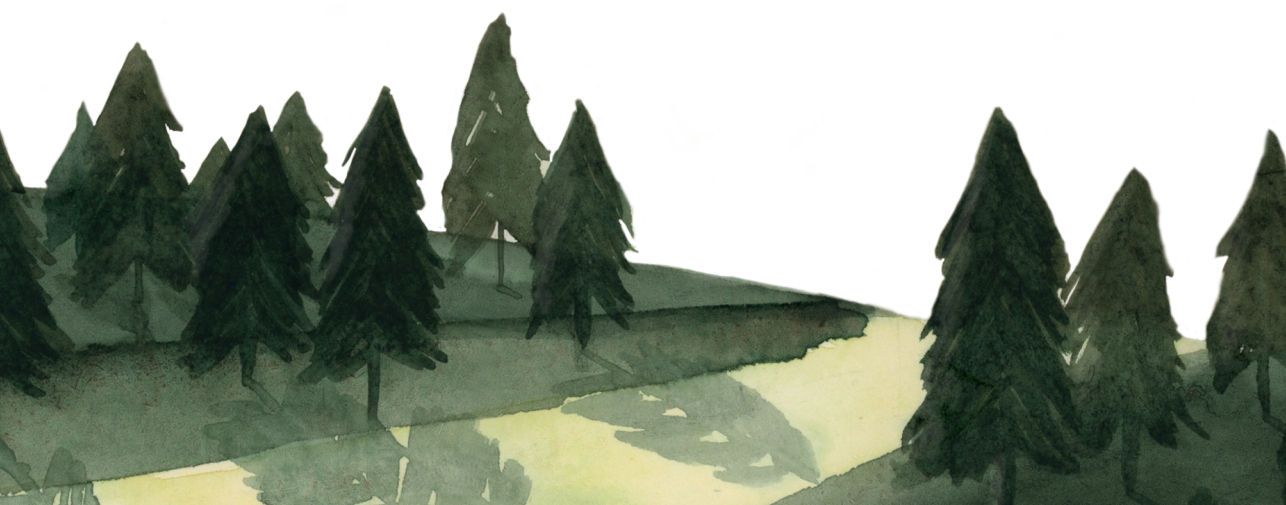
CHAPTER 1

General introduction and outline



SYSTEMIC SCLEROSIS: GENERAL INFORMATION

Systemic sclerosis (SSc) is a severe rheumatic autoimmune disease with a heterogeneous disease course in which multiple organs can be involved (1). With a prevalence of around 4000 patients in the Netherlands, SSc is considered a rare disease (2, 3). The onset of SSc is most common between the ages of 40 and 60 years (1). There is a notable sex discordance, with females affected more frequently than males (4).

A triad of vasculopathy, autoimmunity and fibrosis characterizes the disease (1). Over 95% of SSc patients have Raynaud's phenomenon, which occurs due to episodic, reversible vasospasm after exposure to cold or stress leading to pain and temporary discoloration of the fingers and toes. Raynaud's phenomenon strongly affects quality of life (5-7), and is often the first sign of the disease. Alterations of the microvessels can be detected by nailfold capillaroscopy (8, 9). Dysregulation of the immune system is clear as in 95% of the SSc patients anti-nuclear antibodies are present (10). Anti-centromere (ACA; also known as anti-CENP-B), anti-topoisomerase I (ATA; also known as anti-Scl-70), and RNA-polymerase III antibodies are the most disease specific and common anti-nuclear antibodies in SSc (11, 12). Fibrosis, the third element of the triad, is most visible in the skin, and patients are classified as non-cutaneous (without skin fibrosis), limited cutaneous (skin fibrosis of the face and distal to elbows and knees) and diffuse cutaneous (skin fibrosis affecting either the thorax, abdomen or extremities proximal to elbows and knees) (13). The myocardial, lung, and gastrointestinal tissues are also frequently affected by fibrosis (Figure 1). The extensive multiorgan involvement leads to a high morbidity and mortality, exceeding those of the general population and other rheumatic diseases (14).

Over the past few decades, there have been substantial advances in the understanding and management of SSc. In order to improve the care for SSc patients, we need to know the current state of the art in terms of basic (pathophysiology) and clinical (diagnosis, treatment and monitoring of outcomes) research. To these ends, data from the Leiden Combined Care in SSc (CCISS) cohort (15) will be used in this thesis and is the starting point of this introduction.

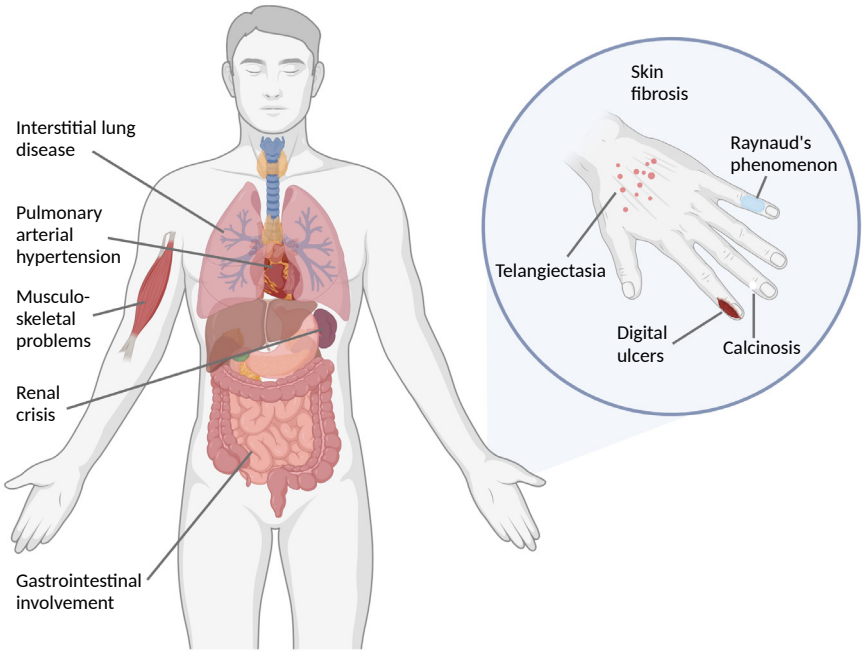


Figure 1. Organ involvement in SSc

Created with BioRender.com. Adapted from: Systemic Sclerosis. Nature Reviews, 2015.

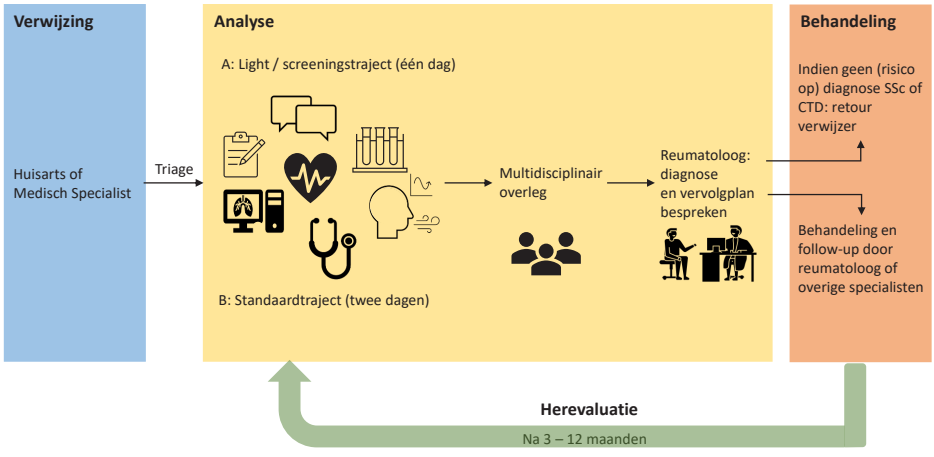


Figure 2. Evaluation procedure of patients visiting the Care Pathway for Raynaud's phenomenon, systemic sclerosis and connective tissue diseases at Leiden University Medical Center

Adapted from de Medische Metrolijn Systemische Sclerose en Connective Tissue Disease (Dr. J.K. de Vries-Bouwstra en Mw. K. van Doorn).

STARTING POINT: LEIDEN CCISS COHORT

The CCISS cohort from Leiden University Medical Center (LUMC) in the Netherlands is a prospective SSc cohort (15). Since its beginning in 2009, the CCISS cohort has included SSc patients in accordance with the ACR/EULAR 2013 classification criteria for SSc (16), which enables the inclusion of mild and early cases. As of January 1st 2022, 1077 patients have been screened, of whom 708 fulfil the ACR/EULAR 2013 SSc criteria.

The CCISS cohort is linked to an annual care pathway for the included patients, shown in Figure 2. The care pathway consists of a 1-to-2-day program at the LUMC. The goal of this care pathway is to screen for organ involvement and, depending on the individual patient's health status, to recommend or start therapy.

Prior to the care pathway visit, patients are asked to complete multiple online questionnaires focusing on quality of life, symptom burden and functional ability. At the visit to the hospital, all patients have a consultation with a physician or advanced nurse practitioner, a specialized rheumatology nurse and a physical therapist. Moreover, blood and urine samples are taken; and patients have an electrocardiogram and pulmonary function test. On indication, patients can have consultations with a pulmonologist, cardiologist, gastro-enterologist, occupational therapist, dietician, or social worker, or have additional examinations including chest imaging, exercise tests, echocardiography, or right heart catheterization. The multidisciplinary team then discusses each patient resulting in specific advice on either (diagnostic) follow-up, initiation, switching or stopping of medications and referral to additional medical consultation or evaluation by other healthcare professionals. All these data are systematically collected in an online database.

Because of this routine assessment and data collection, the CCISS cohort has a standardized and extensive follow-up with high data completeness in an unselected SSc cohort. As such, this cohort offers a unique opportunity to study all of the aforementioned aspects in SSc, and will therefore be the starting point to address five crucial steps on the road to better care for SSc.

STEP 1: CLASSIFICATION AND IDENTIFICATION OF (VERY) EARLY SSC PATIENTS

Identifying very early SSc patients is of the utmost importance to start treatment promptly. Indeed, early intervention was shown to improve the disease course and outcomes in SSc and other inflammatory rheumatic diseases (17, 18). Classification criteria can aid in the early identification required for early interventions, and also improve the quality of research by stimulating uniformity of cohorts. To enable early identification of SSc patients, uniform classification criteria are needed that accurately identify patients with early SSc, which is outlined in step 1.

The first classification criteria for SSc were published in 1980 with skin fibrosis as a major criterion (19). These criteria had a high specificity but low sensitivity to identify SSc patients early in the disease course and with limited SSc (20, 21). In 1988, LeRoy *et al.* presented new criteria for limited and diffuse cutaneous SSc, which were also centred on skin involvement (22). Building upon previous criteria, the ACR/EULAR 2013 criteria (Figure 3) added emphasis to the vascular manifestations (16). Items such as sclerodactyly, puffy fingers, telangiectasia, digital ulcers, pitting scars, pulmonary arterial hypertension, interstitial lung disease, Raynaud's phenomenon, abnormal nailfold capillaroscopy and SSc-related autoantibodies were included in these new criteria, with each a score of 1 to 4 points. The ACR/EULAR 2013 criteria are fulfilled if patients have ≥9 points. Application of these criteria has improved the classification of individuals early in the disease course, and with the limited cutaneous subtype or mild forms of SSc (23).

Recently, efforts have been made to identify patients even before progressing to definite SSc (=fulfilling ACR/EULAR 2013 criteria). "Very early SSc" was identified as a combination of at least two SSc features, namely Raynaud's phenomenon, puffy fingers, disease-specific autoantibodies, and microvascular alterations detected by nailfold capillaroscopy (24, 25). In 2014, the criteria for Very Early Diagnosis Of SSc (VEDOSS; Figure 3) were formulated. The classification criteria are met when at least two of these four items are present, but the patient has <9 points according to the ACR/EULAR 2013 criteria.

The VEDOSS cohort consists of a heterogeneous group of individuals at risk of progressing to definite SSc (26). One of the most important risk factors for the development of definite SSc is the presence of the SSc-specific autoantibodies: ATA, ACA and ARA (27, 28). However, not all very early SSc patients develop definite SSc (27, 28). Therefore, there is need to improve prognostication in this group. Given the importance of the SSc-specific autoantibodies for progression to SSc, more detailed characterization of the autoantibody response might increase insights and contribute to improved disease prognostication.

ACR/EULAR 2013 criteria for SSc			**VEDOSS criteria**
Items	Sub-items	Score	
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9	
Skin thickening of the fingers	Puffy fingers Sclerodactyly	2 4	Puffy fingers
Fingertip lesions	Digital tip ulcers Pitting scars	2 3	
Telangiectasia		2	
Abnormal nailfold capillaries		2	Abnormal nailfold capillaries
Raynaud's Phenomenon		3	Raynaud's Phenomenon
SSc-related autoantibodies (anti-centromere, anti-topoisomerase I, anti-RNA polymerase III)		3	SSc-related autoantibodies (anti-centromere, anti-topoisomerase I, anti-RNA polymerase III)

Figure 3. ACR/EULAR 2013 SSc and VEDOSS criteria

Adapted from van Hoogen *et al.* ARD, 2013 and Avouac *et al.* ARD, 2014.

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology. VEDOSS: Very Early Diagnosis Of Systemic Sclerosis.

For ACR/EULAR 2013 criteria for SSc, only count the highest score of the sub-items. Patients having a total score of 9 on the ACR/EULAR 2013 criteria for SSc or more are classified as definite SSc. The VEDOSS criteria are met when at least two of these four items are present, but the patient has <9 points according to the ACR/EULAR 2013 criteria.

STEP 2: ELUCIDATING THE PATHOPHYSIOLOGY OF SSC, IN PARTICULAR THE CONTRIBUTION OF THE SSC-SPECIFIC AUTOANTIBODIES

The pathophysiology of SSc involves an interplay between vasculopathy, autoimmunity and ultimately fibrosis (Figure 4). However, how these three aspects are intertwined remains unclear. Early in the course of SSc, it seems that the pathogenesis consists of microvascular changes leading to endothelial cell damage and a complex autoimmune response involving the innate and adaptive immune systems with autoantibody production (29). The aforementioned endothelial cell damage leads to the opening of endothelial junctions, migration of inflammatory cells, increased capillary permeability, progressive vascular leakage, and eventually to clinical symptoms of vasculopathy and/or an abnormal nailfold capillaroscopy (29, 30). Fibroblasts are the cells that produce elements of the extracellular matrix including collagen, fibronectin and degrading elements. Fibroblasts differentiate into activated myofibroblasts which are responsible for irreversible fibrosis (29).

Elucidating the contribution of these disease-specific autoantibodies and their underlying B cell response in the processes underlying SSc might help to understand whether these antibodies or B cell responses drive disease pathogenesis, which leads to step 2.

Both the innate and adaptive immune systems are heavily involved in the pathogenesis of SSc. A large body of evidence has indicated that the adaptive immune system with autoreactive T cells and autoantibodies produced by B cells plays a central role in the disease processes underlying SSc (29). Indeed, B cell abnormalities have been found in SSc patients, including chronic hyper-reactivity of memory B cells, which leads to expanded naive B cells. This chronic B cell activation induces components involved in the inflammatory and fibrotic pathways of SSc. For example, one of the most important functions of B cells is to produce antibodies which usually bind to pathogens (=foreign substances) to neutralize them (31). In SSc, nearly all patients have detectable antinuclear antibodies, which are antibodies against compounds found in the body's own nuclei. At least 9 different nuclear antigens have been described. The co-existence of the B cell responses targeting these antigens is rare (10, 32). The B cell responses targeting topoisomerase 1 (ATA), centromere proteins (ACA) and RNA polymerase III (ARA) are most commonly observed in SSc patients (12, 33). All three SSc-specific autoantibodies are associated with distinct clinical phenotypes, which observation has led to the question whether autoantibodies also contribute to the pathogenesis of SSc next to their prognostic value (34).

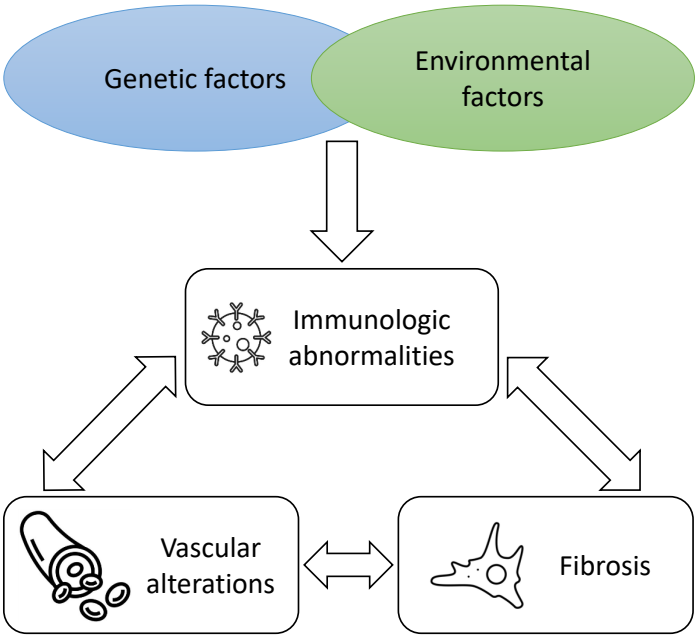


Figure 4. Schematic overview of the pathophysiology of systemic sclerosis

Adapted from: Katsumoto *et al.* Annu Rev Pathol. 2011

STEP 3: RISK STRATIFICATION

Due to the heterogeneity of the disease, the clinical approach should be tailored to the individual patient. Risk stratification is a key element of this, outlined in step 3.

The various autoantibodies provide ample opportunity to do so, as ACA and ATA are associated with distinct clinical phenotypes. The expression of ATA is strongly associated with the occurrence of diffuse cutaneous SSc, severe digital vasculopathy and interstitial lung disease (ILD) (35-38). The presence of ACA, on the other hand, is associated with limited cutaneous SSc, a higher prevalence of calcinosis and gastro-intestinal involvement (10, 39-41), and the lowest incidence of pulmonary fibrosis, scleroderma renal crisis and cardiac involvement (42). Additionally, ACA positive SSc patients generally have a better prognosis and survival than ATA-positive SSc patients (39, 42, 43). However, there is a clinical heterogeneity within the autoantibodies. Deeper insights into a more precise risk stratification, perhaps involving a combination of autoantibodies, clinical manifestations and other factors such as disease-specific biomarkers, are warranted to better delineate SSc trajectories and personalize treatment interventions in SSc patients.

Regarding the other factors, the biological sex of a patient and the disease duration can also be used as guidance. Male patients often have a more rapid and severe disease course than female patients (4). Interestingly, male patients also more often have presence of ATA compared to female patients. A possible interaction between ATA, sex and disease outcomes has not been evaluated.

STEP 4: QUANTIFICATION: DISEASE OUTCOMES IN SSC

While biomarkers such as antibodies aid in the prediction of disease course and at the same time might reflect underlying pathophysiology, currently, we face the situation where we still have a lack of treatments that effectively target each organ domain reducing damage accrual and resulting in improved quality of life and lower mortality. Indeed, besides increased risk of mortality, SSc patients can be burdened by substantial physical disability and significantly impaired Health-Related Quality of Life (HRQoL).

Physical functioning, as reflected by functional assessments, is strongly associated with changes in HRQoL over time (5). To offer optimal support to those patients in whom SSc has important impact on everyday life and daily activities we need to gain insight in factors affecting HRQoL. Insight in the longitudinal course of functional disability in SSc patients and identification of patients who progress in functional disability can guide health care in SSc.

STEP 5: MANAGEMENT OF SSC: OPTIMIZING NON-PHARMACOLOGICAL CARE IN SSC

Finally, the fifth and last step: to improve the present care of SSc patients. This thesis will focus on the nonpharmacologic aspect thereof.

Consequentially to the clinically heterogeneous character of this disease, optimal care requires a multidisciplinary approach. Thus, apart from medical care, nonpharmacologic care is an essential element in the management of SSc. A wide range of nonpharmacologic interventions in SSc is used, provided by health care providers with various professional backgrounds including nurses, physical or occupational therapists, social workers, or psychologists (44). Health professionals in rheumatology are trained and skilled regarding the holistic approach to support patients and address their problems (45). Although the importance of nonpharmacologic care in the management of SSc is widely recognized, unmet needs regarding nonpharmacologic care are reported by a high proportion of patients (46-48). Furthermore, the scientific base of many nonpharmacologic interventions is limited. The next part of this thesis will focus on two interventions that are commonly used in patients with SSc: gloves and physical therapy.

To decrease the burden of Raynaud's phenomenon, patients are often advised to protect themselves against the cold (49-51), amongst others by wearing gloves (52, 53). Regarding the type of gloves, in particular, the use of gloves containing silver fibres is promoted by health professionals (52, 53). However, the additional benefit of the silver fibres gloves over normal gloves has not been demonstrated in SSc.

Over half of the SSc patients receive physical therapy in a one-year period (54-56). In general, physical therapy is aimed at preventing and decreasing functional disability by improving and/or maintaining aerobic capacity, muscle strength and endurance, range of motion, mobility and flexibility and providing adequate information, advice and education on self-management, in particular lifestyle modifications. Promotion of physical activity, according to public health recommendations, is an important aspect of life style education.

The scientific evidence underpinning the effectiveness of various physical therapy treatment modalities is relatively scarce. To date, three literature reviews suggested that, in general, exercises in SSc are safe and beneficial based on a limited number of studies (57-59). However, these reviews did not evaluate methodological quality of the included studies and did not distinguish between the different types of exercise, which is needed to identify the gaps in knowledge, to plan future research projects and to develop specific guidelines for physical therapists.

To improve the quality of physical therapy care for SSc patients, we must overcome a number of bottlenecks. Apart from the abovementioned lack of evidence on the effectiveness and safety of physical therapy in SSc, improving the quality of physical therapy care for SSc patients is also challenging due to a lack of insight into physical activity behaviour and the delivery of physical therapy in daily practice. With this, it should be acknowledged that physical therapy treatment is often provided in primary care, where expert knowledge on this rare condition is not largely available. Given this observation, knowledge on how physical therapists in primary care and medical specialists and other health care professionals in the hospital can best collaborate would be very helpful, yet insight is currently lacking. Another prerequisite to improve physical therapy is adequate training on SSc for physical therapists.

AIMS AND OUTLINE OF THIS THESIS

As indicated by this introduction, the care for SSc patients can be improved in various areas. The aim of this thesis is to explore different roads to improve care for SSc patients, following the five steps outlined in the introduction: step 1 and 2 (identification and elucidation), step 3 and 4 (stratification and quantification) and step 5 (optimization).

Step 1 and 2 will start with a literature review on the contribution of the autoreactive B cell responses targeting nuclear antigens to the pathogenesis of SSc in **chapter 2**. We will then focus on the expression of ATA in the next chapters, starting with the role of ATA in suspected very early SSc patients. However, we have not been able to identify suspected very early ATA-positive SSc patients in our cohort. Therefore, in **chapter 3**, we will conduct a literature review on the prevalence of the SSc-specific autoantibodies and clinical characteristics of suspected very early SSc patients. To tackle the problem of few suspected very early ATA-positive SSc patients, we will assess time between onset of RP and first non-RP symptom as a proxy for progressing to definite SSc in ATA-positive patients. In **chapter 3**, we will investigate the hypothesis that a shorter time between RP and first non-RP symptom is associated with higher ATA levels and more severe disease.

Elucidating the disease pathophysiology is a long and winding road. Therefore, it is important to simultaneously critically evaluate and improve the current management of SSc patients. For that, we need **step 3 and 4**: risk stratification and quantification (monitoring outcomes). Just like ATA, the male sex is also a subset within SSc with a worse prognosis. Interestingly, male SSc patients more often express ATA compared to female patients. In **chapter 4** we will evaluate this so-called "sex prevalence and severity paradox" in SSc by assessing the sex specific risk of ATA expression on mortality and the development of diffuse cutaneous SSc, severe interstitial lung disease and pulmonary hypertension in SSc patients from two different cohorts. For the quantification, a closer look at the Leiden CCISS cohort over the last ten years will be taken in order to address two study aims. First, in **chapter 5** disease outcomes over time will be evaluated by using the cohort entry year of SSc patients as a grouping variable. Second, it is important to gain insight into the functional disability of SSc patients. Therefore, the Health Assessment Questionnaire (HAQ) over time in SSc patients will be investigated in **chapter 6**.

Then, improvement of the quality of nonpharmacologic care in SSc will be addressed in **step 5**. A widely used example of nonpharmacologic care is the use of silver fibre gloves to reduce the burden of Raynaud's phenomenon in SSc patients. In **chapter 7**,

the effect of the silver fibre gloves will be compared to normal cotton gloves in SSc patients using a multicentre, double-blind cross-over randomized trial. From **chapter 8** onwards, optimization of physical therapy care in SSc patients will be studied. First, the levels of physical activity in SSc patients will be evaluated in **chapter 8**. Second, a systematic literature review will be performed to assess the safety and effectiveness of exercise therapy in SSc in **chapter 9**. Third, the current usage and contents of, and need and preferences regarding physical therapy care in SSc will be evaluated, from both the perspective of the SSc patients in **chapter 10** as well as their treating physical therapists in **chapter 11**. Fourth and last, **chapter 12** will explore the communication between primary care physical therapists, patients and expert centres and the preferences for a postgraduate training on SSc for physical therapists using focus groups.

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