# INVESTIGATION OF ARTICULAR DISEASE ACTIVITY AND HAND INVOLVEMENT IN SYSTEMIC SCLEROSIS

Ph.D. Thesis

**Veronika Lóránd, MD**
Department of Rheumatology and Immunology
University of Pécs, Medical Centre, Pécs Hungary

**Supervisor: Cecília Varjú, MD, Ph.D.**
Department of Rheumatology and Immunology
University of Pécs, Medical Centre, Pécs Hungary

Program: B-372; Immunological and clinical aspects of polysystemic autoimmune conditions
Program leader: László Czirják, MD, Ph.D., D.Sc.

Doctoral School: Theoretical Medical Sciences
Leader of the Doctoral School: László Lénárd, MD, Ph.D., D.Sc.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Anti-CCP | anti-cyclic citrullinated peptide |
| CoC28 | number of contractures in the joints of the 28 joint count |
| CDAI | Clinical Disease Activity Index |
| CHFS | Cochin Hand Function Scale |
| CRP | C-reactive protein |
| DAIs | disease activity indices |
| DAS28-CRP | Disease Activity Score of 28 Joints using CRP |
| DAS28-ESR | Disease Activity Score of 28 Joints using ESR |
| dcSSc | diffuse cutaneous systemic sclerosis |
| DIP | distal interphalangeal joint |
| DLCO | diffusing capacity of the lung for carbon monoxide |
| EScSG-AI | European Scleroderma Study Group Activity Index |
| ESR | erythrocyte sedimentation rate |
| EUSTAR | European Scleroderma Trials and Research Group |
| FTP | Finger to Palm distance |
| FVC | forced vital capacity |
| HAI | Hand Anatomic Index |
| HAMIS | Hand Mobility in Scleroderma test |
| HAQ-DI | Health Assessment Questionnaire Disability Index |
| HRCT | high-resolution computer tomography |
| ICC | intraclass correlation coefficient |
| JSC | joint swelling count |
| JTC | joint tenderness count |
| lcSSc | limited cutaneous systemic sclerosis |
| MCP | metacarpophalangeal joint |
| MSAI | Modified Scleroderma Activity Index |
| NA | not applicable |
| ND | not done |
| NS | not significant |
| OMERACT | Outcome Measures for Rheumatoid Arthritis Clinical Trials |
| PIP | proximal interphalangeal joint |

| | |
|---|---|
| qDASH | Quick Questionnaire of the Disability of the Hands, Arms and Shoulders |
| RA | rheumatoid arthritis |
| RF | rheumatoid factor |
| RP | primary Raynaud's phenomenon |
| SD | standard deviation |
| SDAI | Simplified Disease Activity Index |
| SF36 | 36-Item Short Form Health Survey |
| SF36 MCS | SF36 Mental Component Summary |
| SF36 PCS | SF36 Physical Component Summary |
| sHAQ | Scleroderma Health Assessment Questionnaire |
| SSc | systemic sclerosis |
| US | ultrasound examination |
| VAS | visual analogue scale |
| vs. | versus |

# 1. INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterised by autoimmune phenomena, generalised vasculopathy and fibrosis. Its heterogeneous manifestations include skin, musculoskeletal, and internal organ involvement. The cardiopulmonary, renal and gastrointestinal manifestations are the main causes of mortality, while skin and musculoskeletal involvement mainly cause disability and reduce quality of life [1, 2].

The severity of a systemic connective tissue disease is determined by disease activity, the potentially reversible phenomena of the disease and by the irreversible organ damage. The main therapeutic goal in the management of rheumatic diseases is reducing disease activity in order to minimize damage.

On the ground of joint inflammation and fibrotic processes contractures evolve early in the course of the disease, mostly affecting the hands. Currently there is very limited evidence based therapy for arthritis in SSc. Moreover, there is an unmet need for validated tools to measure joint related disease activity in both clinical practice and in drug trials [2].
In the management of RA the "treat to target" attitude [3-5] was facilitated by the development and validation of simple tools measuring disease activity such as the Disease Activity Score of 28 Joints using Erythrocyte Sedimentation Rate (DAS28-ESR) [6, 7].

Similarly to RA, articular involvement, such as joint swelling, tenderness, morning stiffness and contractures primarily affect the hands in SSc. The Cochin Hand Function Scale (CHFS) is a patient self-assessment questionnaire that allows quick and efficient measurement of hand function and disabilities regarding activities of daily living [8].

Our aim was to analyse articular disease activity as well as to validate tools for measuring joint involvement in SSc focusing on the hands.

# 2. BACKGROUND

## 2.1. Hand involvement in SSc

### 2.1.1. Causes, symptoms and signs

Skin and articular involvement in SSc are usually most prominent on the hands [1, 9]. The numerous different aspects of hand involvement of SSc are summarised in Table 1.

**Table 1 Aspects of hand involvement in systemic sclerosis**

| | Articular manifestations | Non-articular skeletal manifestations | Tendon related manifestations | Skin, soft tissue and vascular manifestations | Neural manifestations |
|---|---|---|---|---|---|
| **Complaints** | - joint pain<br>- joint stiffness | - shortening and loss of fingers | - pain over the tendons | -recurring wounds on fingertips<br>-painful scars on fingertips<br>-puffy fingers<br>-tightening of the skin | - numbness<br>- ischemic pain<br>- clumsiness |
| **Symptoms** | - joint tenderness and/or swelling (arthritis)<br>- joint contractures | | - tendon friction rubs | - ischemic digital ulcers<br>- digital gangrenes<br>- scleroedema<br>-sclerodactylia | - hypoesthesia<br>- anaesthesia |
| **Signs (laboratory, imaging, histology)** | - elevated acute phase reactants<br>- joint space narrowing<br>-marginal erosions<br>- synovial proliferation<br>- synovial effusion | - generalized osteoporosis or osteopenia<br>- acroosteolysis and other localized bone resorption<br>-osteomyelitis | - teno-synovitis<br>- carpal tunnel syndrome | - elevated acute phase reactants<br>- calcification on radiography | |

### 2.1.2. Disability and quality of life

Johnson *et al* [10] found that joint involvement is more disabling in SSc than in psoriatic arthritis, and patients with SSc experience more severe pain than patients with RA. Physical health related to quality of life is adversely affected in patients with SSc and disability is strongly associated with the joint involvement. In the Canadian National Survey among more than 400 patients with SSc, complaints related to decreased hand function were frequently endorsed (67% of the patients), and were commonly associated with remarkable impact on daily activities [11]. In our recent multicentre study of 944 patients with SSc dyspnoea, pain, digital ulcers, muscle weakness and gastrointestinal symptoms were found to be the main factors driving level of disability in multiple regression analysis of SHAQ [12]. In diffuse cutaneous SSc (dcSSc) the development of functional impairment is quite fast, significant functional impairment is present in about half of the patients within the first 18 months after onset of the disease [13].

Health related quality of life perceived by patients with SSc is significantly impaired compared with healthy individuals. [14] Moreover, patients with SSc have impaired health related quality of life in comparison with RA, SLE, and Sjögren patients, when age, pain, psychopathology, and coping strategies are taken into account [14].

### 2.1.3. Tests and patient self-assessment questionnaires

Several questionnaires have been developed in order to measure hand function, quality of life, and global disability of rheumatic patients. Some of these have been primarily developed for SSc, others have been adapted to SSc or validated for SSc from other diseases without any changes. Clements *et al* [2] evaluated the validity of various potential outcome variables for the assessment of articular involvement according to the Outcome Measures for Rheumatoid Arthritis Clinical Trials (OMERACT) filter. Here we will only briefly introduce the Health Assessment Questionnaire Disability Index (HAQ-DI), which is undoubtedly the most important instrument in measuring disability in SSc. HAQ-DI is a patient questionnaire that has been fully validated in SSc and translated into many languages [15, 16]. In the high-dose versus low-dose D-penicillamine study [13] it has also been shown, that HAQ-DI correlates with disease outcome in SSc. Rannou *et al* [17] showed that hand disability was the far most important determinant of disability measured by HAQ-DI in SSc.

Table 2 is a brief summary of the tests related to disability; hand involvement and health related quality of life in SSc.

**Table 2 Tests related to disability, hand involvement and health related quality of life in systemic sclerosis**

| Name of test | Objective of test | Type of test |
|---|---|---|
| Health Assessment Questionnaire Disability Index[18] | overall disability | patient self-questionnaire |
| Scleroderma Health Assessment Questionnaire [19] | overall disability | patient self-questionnaire |
| Hand Anatomic Index[20] | structural hand impairment | physical examination |
| Modified Hand Anatomic Index[21] | structural hand impairment | physical examination |
| Finger to Palm distance[22] | structural hand impairment | physical examination |
| Delta Finger to Palm distance[22] | structural hand impairment | physical examination |
| Disability of the Hands, Arms and Shoulders[23] | disability of the upper extremities | patient self-questionnaire |
| Cochin Hand Function Scale[8] | hand related disability | patient self-questionnaire |
| Michigan Hand Questionnaire[24] | hand related disability | patient self-questionnaire |
| Hand Mobility In Systemic Sclerosis[25] | hand mobility | performance test |
| Modified Hand Mobility In Systemic Sclerosis[26] | hand mobility | performance test |
| Arthritis Hand Function Test[27] | hand strength and dexterity | performance test |
| 36-Item Short Form Health Survey [17] | health related quality of life | patient self-questionnaire |
| World Health Organisation – Quality of life Short Form questionnaire [28] | quality of life | patient self-questionnaire |

## 2.2. Articular involvement in SSc

Articular involvement can be present in SSc in many different forms. The most common manifestations are arthralgia and joint contractures. Arthritis, characterised by morning stiffness, joint tenderness and swelling is less frequent, but also relatively often present in SSc [11, 29]. Radiologic signs of joint inflammation, such as joint space narrowing and erosions are also quite common in patients with SSc. Joint involvement can be the initial manifestation of SSc. Its onset can be acute or insidious with an intermittent, chronic remittent, slowly progressive, or rapidly progressive course. It can be present in a monoarticular, oligoarticular, or polyarticular pattern [30]. Though involvement of the hands is more prominent and frequent in SSc than the feet, foot involvement should also be taken into consideration [31-35]. The involvement of the temporomandibular joints in SSc has also been reported in a few studies [35-37].

### 2.2.1. Prevalence

Articular involvement is very common in SSc. However, only the average frequency can be estimated, partly because of the difficulties of physical examination, partly because of the lack of consensus on assessment techniques. In the European Scleroderma Trials And Research group (EUSTAR) database frequencies of synovitis, tendon friction rubs, and joint contractures were 16%, 11%, and 31%, respectively [29].

The prevalence of arthralgia in consecutive patients with SSc differs greatly, from 23 to 81%, among the studies. However, it is mainly reported in about 70% of the patients [11, 17, 30-33, 38-44].

The frequency of synovitis in SSc by clinical assessment is around 15-20% [29-33, 38, 39, 41]. In consecutive patients with SSc the mean number of tender joints is around 3; the mean number of swollen joints is between 0 and 2 according to most studies on this issue [45-49], except for the study of Blocka *et al* [31], were this number was much higher. According to a recent meta-analysis of 7 studies [50] the prevalence of radiologically detectable arthritis is 26% in SSc.

There is no consensus on what degree of decrease in range of motion should be called a joint contracture. Therefore, the prevalence of contractures assessed by physical examination in different studies varies between 24 and 56 % [13, 51].

### 2.2.2. Clinical symptoms

Synovitis can be present in patients with SSc in all disease stages, but it is most frequent in the early stage of the disease. The frequency of synovitis is higher among patients with dcSSc compared to patients with limited cutaneous subtype (lcSSc); but only in early disease [29, 49, 52]. Arthritis-related pain is closely associated with SSc patients' health related quality of life [14]. According to Baron *et al* [30] arthritis can be detected most often in the metacarpophalangeal joints (MCP), wrists, knees, distal interphalangeal joints (DIP), and proximal interphalangeal joints (PIP), in decreasing order.

Arthralgia was found to be significantly more common in patients with dcSSc, than with lcSSc.[41] In a Canadian self-administered online survey of 464 patients with SSc, complaints related to impaired hand function were reported by about three-quarter of the patients. More specifically, impaired hand function including hand stiffness and joint-pain were found in 81% while swollen joints in 61% of the cases [11]. Moreover, Skare *et al* [44] reported that pain and stiffness were the symptoms that most affected functionality.

Contractures are one of the main sources of disability in SSc. They are frequent in both subtypes; however, the prevalence of joint contracture is higher in dcSSc, than in lcSSc. Moreover, diffuse cutaneous subset is an independent predictor of the progression of flexion contractures. Though the development of contractures is relatively slow and gradual, it can be present in the early stages of the disease, too [39, 41, 46, 52, 53].

### 2.2.3. Physical and laboratory examination

The assessment of arthritis is very difficult in SSc due to certain characteristics of the disease: skin oedema, thickening and tethering of the skin, digital ulcers, subcutaneous calcinosis and contractures [48] Concerns have been raised that physical examination without radiological examination might not by sensitive enough to assess arthritis in SSc [48, 54, 55]. So far, there is no fully validated and universally accepted assessment technique for assessing arthritis in SSc by physical examination. The 8 joint count has been used in a few studies [40, 45-47, 49, 56]. This assesses swelling and tenderness of the MCPs (as a whole on each hand), the wrists, elbows, and knees as absent or present. The 28 joint swelling and tenderness count – as part of the DAS28-ESR – is a worldwide accepted tool for assessing arthritis in RA [5, 57]. This particular instrument has also been used in SSc in two studies [56, 58], although its validity has not yet been proved in this disease.

The association of acute phase reactant elevation – indicating systemic inflammation – and the arthritis detected by physical evaluation, radiography, MRI, US and Doppler US have been reported by a number of studies [29, 48, 52, 53, 59, 60]. Moreover, in the study of the EUSTAR cohort of 7286 patients with SSc, clinical synovitis had the highest strength of association with elevated acute-phase reactants taken as the dependent variable. This was true in both the lcSSc and the dcSSc subsets and in all disease stages [29]. The radiographic signs of joint inflammation, as joint space narrowing and marginal erosions are also associated with an increased C-reactive protein (CRP) level [53]. However, it must be noted, that CRP elevation is a marker of current inflammation, while marginal erosions, juxtaarticular osteoporosis and joint space narrowing are signs of long term inflammation that is not necessarily present at the moment [34].

The adaptation of DAS28-ESR to SSc may be considered, because the joint involvement pattern of SSc may differ from that of RA. Unlike RA, the DIP joints are often involved in SSc, as erosions and joint space narrowing are frequently seen on hand X-ray. However, the presence of concomitant osteoarthritis cannot be excluded, either [30, 52, 53]. Besides DAS28-ESR, the adaptation of other articular indices – used in RA – may be considered for joint assessment in SSc, e.g. the Disease Activity Score of 28 joints using CRP (DAS28-CRP), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI).

### 2.2.4. Imaging

A number of studies have been carried out regarding imaging of SSc joint involvement. Radiographic studies are the most common, but there are also a few studies about ultrasound imaging (US), magnetic resonance imaging (MRI), thermography and bone scanning [30-35, 38, 50, 52-55, 59, 61-67]. The most frequent articular findings by imaging were joint space narrowing, erosions, and contractures.

In the study of Blocka *et al* [31] all radiographic findings showed progression, although isolated reversibility was also noted. In the longitudinal study of Avouac *et al* [62] radiographic progression of erosive arthritis was seen in 24%, progression of acroosteolysis in 22% and deterioration of flexion contractures in 18% of the patients over a median of 5-year follow-up period.

Though joint space narrowing can be a sign of previous synovitis, it can also be the consequence of osteoarthritis. Joint space narrowing in SSc is most frequently seen in the

DIPs, but it is also common in the other hand joints. It is not clear, whether the high frequency of joint space narrowing in the DIPs of patients with SSc is part of the articular manifestations of scleroderma or if it is caused by concomitant osteoarthritis of the hands [30, 53]. In the US study of Cuomo *et al* [59], patients with SSc displayed a significantly lower prevalence of joint space narrowing than patients with RA. In terms of SSc cutaneous subsets, Erre *et al* [53] found no significant differences in the prevalence of joint space narrowing.

Erosions in SSc are often similar to those seen in RA, however they are less frequent [35, 59]. Nevertheless, in SSc well-circumscribed foci of osseous resorption or erosions on the dorsal aspects of metacarpal or proximal phalangeal heads can be also found [31]. Erosions are most frequently detected in the PIP and MCP joints, however erosions can be present in the DIPs, too [30, 48, 52, 53]. Avouac *et al* [52] reported that 72 % of the patients with erosions had erosive changes in the DIP joints. It must be noted, that most of their patients were post-menopausal women, therefore the possibility of an arthropathy, unrelated to SSc could not be ruled out. In contrast to this, Blocka *et al* [31] found no erosions in the DIPs in their study. The reason for the differences in these studies might be due to the fact, that assessment of erosions in the DIP joints is particularly difficult.

Cuomo *et al* [59] reported that the prevalence of joint effusions did not differ between patients with SSc and RA, but patients with SSc displayed a significantly lower prevalence of synovial proliferation and power Doppler signal. They found joint effusions and synovial proliferation in 22%; while synovial proliferation altogether in 42% of 45 consecutive patients with SSc. Elhai *et al* [48] detected inflammatory synovitis by US in more than half of the 52 consecutive patients with SSc. Synovitis by US was found in the wrists and hand joints of patients with SSc without a statistically significant difference when compared to the patients with RA. They have also reported that SSc patients with disease duration of 3 years or less had significantly more clinical synovitis than those whose disease duration was more than 3 years; however, the prevalence of US synovitis was not significantly different between the early and the late disease stage groups [48].

Flexion contractures emerge as the most frequent articular abnormality on radiographs in SSc, they are present in nearly 90% of all patients [31]. The prevalence of finger flexion contractures is significantly higher in patients with dcSSc compared with lcSSc [33, 52].

Calcium deposits most often occur in the subcutaneous soft tissues; however, they may also develop in the tendons, peritendinous or periarticular areas [63]. In the study of Cuomo *et al* [59] osteophytosis was detected in 58 %, and periarticular calcinosis in 27% of

the patients with SSc by US. They found no difference in the prevalence of osteophytes in patients with SSc and patients with RA. Erre *et al* [53] – in agreement with Avouac *et al* [52] – reported association between calcinosis and erosions; nevertheless, they were not able to demonstrate a complete topographic overlapping of these lesions. Consequently, the pathogenic role of calcinotic deposits on the occurrence of erosive arthritis is not completely sustained by these results.

Similarly to erosions and joint space narrowing, juxtaarticular osteoporosis and osteopenia are periarticular signs of long term joint inflammation. The prevalence of juxtaarticular osteoporosis detected by radiography is between 4 and 42% [30, 31, 33, 38, 53, 68]. No significant difference was detected in the frequency of juxtaarticular osteoporosis between lcSSc and dcSSc [53]. The similar prevalence of juxtaarticular osteoporosis in the two subsets indicates that subclinical inflammation of the joints is as frequent in lcSSc, as in dcSSc.

The resorption of the distal phalanges, also called as acroosteolysis, is quite common is SSc, with a frequency of 9-63%. Although it is mostly progressive, there is evidence of improvement in a few cases [35]. It is not clear whether its frequency differs among the limited and diffuse cutaneous forms of the disease or not [38, 41, 53, 66]. It is usually studied by radiography; however, Freire *et al* [63] recently reported that sensitivity of US was similar to radiography in acroosteolysis detection. In their study, the majority of patients with tuft resorption also exhibited power Doppler US signal adjacent to the acroosteolysis bed, in some cases even when distal vascularization was not detected. They suggested this might be secondary to granulation tissue to induce bone formation in an attempt to repair the osteolysis.

While resorption of distal phalanges is the most common, osteolysis in other sites including feet, ribs, and mandibles may also occur. In the study of Bassett *et al* [35] seven of 55 patients exhibited partial destruction of ribs 2-6, and 6 of the 35 patients presented with osseous resorption around the mandibular angles. Resorption of the distal ulna was reported in 2% of the patients in three newer studies, while previously it was found in 8% of the patients in the study of Baron *et al* [30, 32, 48, 52].

Positron Emission Tomography/Computer Tomography (PET/CT) is a promising tool to assess arthritis in connective tissue diseases, because of the fluorodeoxyglucose-18 uptake reflects the articular disease activity. Joint swelling had a positive association with the maximum standardized uptake value. A recent study using PET/CT technic showed that

patients with SSc tended to show strong and multiple joint fluorodeoxyglucose-18 uptake [69].

Although joint involvement in SSc can be thoroughly assessed by the various imaging technics described above, regular detailed examination of joints in everyday clinical practice does not seem feasible by either of these technics. Detailed assessment of the joints on radiographs or by ultrasonography is rather time-consuming, while the newer technics, such as PET/CT and MRI are also very expensive and rarely available.

### 2.2.5. Prognostic value of joint involvement

The presence of arthritis was found to be associated with markers of severe vascular (elevated systolic pulmonary arterial pressure > 40 mm Hg) and muscular involvement (muscle weakness) and with increased HAQ-DI [29, 52]. In contrast, synovitis detected by US did not correlate with HAQ-DI [59]. This disagreement can be explained by the fact, that US might detect not only painful and disabling synovitis, but also subclinical synovial effusions as well.

The resorption of distal phalanges is significantly associated with digital ulcers and extra-articular calcification, interstitial lung disease, reduced forced vital capacity (FVC), oesophagus involvement, and more severe disease [52, 53, 64].

SSc patients with joint contractures are more likely to experience severe vascular and muscular disease, as well as to have elevated acute-phase reactants [29]. Moreover, in our recent study [70] the presence of small joint contractures was defined as an independent risk factor of mortality in SSc. Flexion contractures detected by radiography are reported to be associated with interstitial lung disease, reduced FVC, oesophagus involvement and high HAQ-DI [52, 53].

According to a study of Avouac *et al* [62], the presence of digital ulcers independently predicts progression of acroosteolysis. In multiple logistic regression analysis calcinosis and PAH were associated with acroosteolysis as dependent variables [52].

### 2.2.6. Treatment

There have been very few studies assessing the therapy of synovitis in SSc. In analogy to RA, SSc patients with arthritis are usually treated with disease-modifying anti-rheumatic drugs and corticosteroids. Only limited information is available concerning the efficacy of methotrexate, azathioprine, and mycophenolate mofetil. Su *et al* [49] have found that

methotrexate did not decrease significantly the mean of tender joint count and number of areas affected by tendon friction rubs over the 48-week study. They have observed similar results with an IL-2 inhibitor, rapamycin.

According to the EULAR recommendations [71] consistent with expert opinion, low dose of steroids is commonly used for the treatment of inflammatory arthritis in patients with SSc, however, its efficacy has not been proved in any randomized controlled trial [72]. Corticosteroids should only be given in low dose (≤10mg) and with great precaution due to the risk of inducing renal crisis.

A pilot study conducted by Nacci *et al* [56] suggested that intravenous immunoglobulin might reduce joint pain and tenderness, with a significant recovery of joint function in SSc patients with severe and treatment refractory joint involvement. However, the high cost of intravenous immunoglobulin will probably not allow its extensive use among SSc patients with arthritis. D-penicillamine has been found to be ineffective in the treatment of SSc arthritis in a two-year, double blind, randomized controlled clinical trial [40].

Cyclophosphamide was reported by two randomized, controlled clinical trials to be effective in the treatment of SSc related interstitial lung disease [73, 74]. However, there were no differences in musculoskeletal measures (joint swelling, joint tenderness, large joint contractures, muscle tenderness, muscle weakness, fist closure) between the cyclophosphamide and placebo groups at baseline, 12 and 24 months in the Scleroderma Lung Study [46].

In a pilot study of a small group of patients, tocilizumab and abatacept appeared to be safe and effective on joints, in patients with refractory SSc [58].

Tumor necrosis factor alpha inhibitors appeared to be efficient in the treatment of SSc joint involvement in two small studies [75, 76], but did not show clear benefit in a third study [77]. However, according to the consensus of the EUSTAR experts, their use should be limited to clinical trials due to the potential danger of severe exacerbation of pulmonary fibrosis [78].

In cases of marked damaged, hand function may be significantly improved by surgery in some patient. Pain reduction can also be a surgical goal in some cases [79]. There are no drugs available so far that have been proven to improve calcinosis [72].

### 2.2.7. Rehabilitation

There have been a few small studies investigating different musculoskeletal rehabilitation techniques in SSc. The main techniques that have been proved to have beneficial effect on the hands are range of motion exercises, paraffin wax bath, connective tissue massage, manual lymph drainage, and patient education [80-86]. Splinting was also studied, however it did not turn out to be useful [87]. Recently studies are not only focused on the rehabilitation of the hands, but also on orofacial rehabilitation and overall rehabilitation programs – consisting of specific and global techniques [80-86].

Mouth opening, functional ability, hand function, and mobility can be improved by overall rehabilitation. The advantages of overall rehabilitation in SSc have been studied in two recent studies with similar results. However, with a few exceptions – e.g. hand mobility, grip strength – these results tend to disappear over a relatively short period of time, within a few months after the end of the rehabilitation programs. Therefore these programs should be either continuous or regularly repeated in order to sustain their benefits [88, 89].

### 2.2.8. Rheumatoid arthritis-scleroderma overlap

Articular inflammation in SSc cannot be discussed without mentioning patients with SSc-RA overlap, because the presence of RA might alter the course and effective treatment of joint involvement in SSc compared to patients without overlapping RA. Since SSc by itself can cause significant articular damage, the determination of SSc-RA overlap is difficult. Similar changes, resembling those seen in RA, are noted in the hand joints of patients with SSc [30, 35]. Hence exact prevalence of true SSc-RA overlap is hard to determine, it was found in 4.6%-5.2% of patients with SSc [90, 91]. However, patients who fulfil the classification criteria of both diseases, SSc and RA are considered as SSc-RA overlap patients. In the study of Misra *et al* [65] 21% of the SSc patients with articular symptoms also had RA-overlap.

Szűcs *et al* [90] reported that SSc-RA overlap patients carried the SSc-associated HLA-DR3 and HLA-DR11 alleles, as well as the RA-related HLA-DR1 and HLA-DR4 alleles in their genetic study of 22 SSc-RA overlap patients.

Many studies have confirmed that there is no significant difference between patients with and without erosive arthropathy on radiography in terms of rheumatoid factor (RF) [30, 34, 52, 53]. Furthermore, synovitis detected by US does not correlate with the presence of the

RF [59]. In contrast, in the study of Jinnin *et al* [91], elevated RF was seen in SSc-RA overlap patients significantly more frequently, than in those without RA.

Anti-cyclic citrullinated peptide antibodies (anti-CCP) can be detected also in patients with SSc, but they are generally less commonly present than in adults with RA [92]. In a few studies significant association has been detected between anti-CCP positivity and the presence of arthritis and marginal erosions. It has been suggested that high titers of anti-CCP antibodies may help to define the diagnosis of SSc-RA overlap syndrome [38, 93-95]. In contrast, Avuac *et al* [52], found no significant difference between patients with and without arthritis or erosions in terms of presence of anti-CCP antibodies. Generini *et al* [96] did not find significant association between anti-CCP positivity and articular involvement either, though it must be noted, that they had a small number of anti-CCP positive patients (n=3). Ueda-Hayakawa *et al* [97] sugested the combined use of anti-CCP, RF and anti-agalactosyl IgG antibodies, because 91% of their SSc–RA overlap patients were positive for two or more of these RA-related antibodies.

In conclusion, RF and anti-CCP antibodies might be more common in SSc-RA overlap patients than in SSc patients without RA. However, the presence of RF or anti-CCP by itself does not give sufficient help in the establishment of RA diagnosis patients with SSc. Their combined presence with anti-agalactosyl IgG antibodies might give further help.

### 2.2.9. Disease activity and musculoskeletal involvement

EUSTAR developed a preliminary disease activity index to be used in patients with SSc [98, 99]. However, the European Scleroderma Study Group Activity Index (EscSG-AI) awaits further validation, as further work is requested to prove its responsiveness. In this particular index, musculoskeletal involvement is represented by the presence of bilateral arthritis. Based on clinical observations, additional clinical parameters that could indicate disease activity related to the musculoskeletal system might be worsening of musculoskeletal symptoms, active myositis, symptoms corresponding to carpal tunnel syndrome and the presence of tendon friction rubs [29, 45, 100]. Definition criteria and consensus assessment methods of these types of involvements are still lacking, therefore it is difficult to define their precise role in the assessment of disease activity.

Attempts were made to improve the EscSG-AI [101]. Regarding the musculoskeletal component of the disease, the value of HAQ-DI, and the change in HAQ-DI was incorporated into the Modified Scleroderma Activity Index (MSAI). The number of contractures also

correlated with both the EscSG-AI and the MSAI. CRP has shown the same association with these two indices [101]. In the study of the EUSTAR cohort of more than 7000 patients, clinical synovitis had the highest strength of association with elevated acute-phase reactants taken as the dependent variable. This was true in both lcSSc and dcSSc subsets [29]. The radiographic signs of inflammation (marginal erosions, juxtaarticular osteoporosis and joint space narrowing) were also associated with an increased CRP in another study [53]. CRP also correlated with the HAQ-DI [102]. Therefore, the elevation of CRP might reflect an underlying musculoskeletal disease activity in SSc.

### 2.3. Summary

Articular involvement is frequent in SSc, causing significant disability. Patients with early disease, diffuse subset, joint complaints or elevated acute phase reactants should be evaluated for arthritis and contractures. Since joint involvement can be the initial manifestation of the disease, SSc should be considered in the differential diagnosis of patients with arthritis, especially in those with other SSc-related features e.g. puffy fingers, antinuclear antibody positivity and nail fold capillaroscopy changes. Contractures start to develop in the very early stage of the disease, so range of motion should be assessed regularly from the first visit of the patients. Patients with joint contractures should be monitored closely for development or deterioration of vascular or muscle involvement. In case of articular complaints, symptoms, or signs, imaging and laboratory examinations (X-ray, US, acute phase reactants) are also needed. Arthropathy in SSc appears to be progressive in most of the cases.

We are still lacking simple, validated tools for following articular disease activity in clinical trials and everyday patient care. Evidence based therapeutic and preventive strategies for musculoskeletal involvement of SSc have not yet been established. Besides low doses of corticosteroids, methotrexate, leflunomide, azathioprine, mycophenolate mofetil are given as off-label drugs in SSc, as we are lacking large, randomised controlled studies assessing these drugs in the treatment of SSc related arthritis.

# 3. AIMS

## 3.1. Investigation of distribution of joint involvement in SSc

Due to the several life threatening manifestations of SSc, research regarding its articular involvement has been limited. However, joint manifestations can cause dramatic deterioration of the patients' quality of life. There is very limited information regarding the distribution of joint involvement assessed by physical examination in SSc. Our aim was to assess the frequency of joint tenderness and swelling among the 28 joints used in the RA joint-count in a single, large centre and also in a multicentre SSc cohort. The question of extending the 28 joint count by the DIP joints in SSc was also addressed

## 3.2. Cross-cultural adaptation and validation of the Hungarian version of the CHFS in SSc and RA

Joint involvement in SSc is the most prominent on the hands. The CHFS is one of the most often used self-assessment questionnaires in SSc, RA and osteoarthritis. This questionnaire measures hand related disability regarding the activities of daily living. It mainly represents hand associated damage (i.e. contractures), rather than and disease activity (i.e. arthritis). It has not yet been validated in Hungarian language. Our goal was to translate, adapt and validate this questionnaire into Hungarian.

## 3.3. Validation of articular disease activity indices (DAIs) in SSc

Joint contractures develop early in the course of SSc due to underling inflammatory and fibrotic processes. Many tools have been validated for the assessment of hand function and damage. However, there is no validated tool for the assessment of inflammatory joint involvement in SSc. The DAS28-ESR and its modified versions (DAS28-CRP, SDAI and CDAI) are often used in clinical drug trials as well as for patient follow-up in clinical practice. They facilitate a treat to target approach in the management of RA [4]. In order to decide whether these tools could be used for patients with SSc as well, we tested their validity for truth, discrimination, and feasibility according to the OMERACT filter in SSc.

# 4. PATIENTS AND METHODS

## 4.1. Investigation of distribution of joint involvement in SSc

### 4.1.1. Study groups and assessments

Investigation of distribution of joint involvement was carried out in two separate SSc patient cohorts: (1) in our single centre SSc cohort and (2) in a multicentre SSc patient cohort as part of the DeSScipher Study.

#### 4.1.1.1. Single centre study

Seventy seven patients with SSc (mean age: 56.3±11.8 years) fulfilling the 2013 ACR/EULAR classification criteria where included from the Rheumatology and Immunology Department, Medical Centre of the University of Pécs, which is a tertiary care unit [103]. The patients were classified into lcSSc and dcSSc subgroups according to the criteria of LeRoy and Medsger [104].

The following exclusion criteria were defined: (1) end stage internal organ involvement (dialysis required, continuous oxygen therapy, estimated left ventricular ejection fraction less than 30% on echocardiography); (2) significant joint pain or disability caused by other disorders (e.g. gout, osteoarthritis, recent bone fracture etc.); (3) inability to cooperate.

Cohort enrichment was performed in order to increase the proportion of patients with early disease (defined in this particular case as disease duration less than four years) and dcSSc. All consecutive patients with early disease fulfilling the criteria above were enrolled into the study during the recruitment period, while enrolment of consecutive patients with long standing disease was stopped after reaching a predefined number of patients (n=55).

Forty consecutive patients with RA (mean age ± SD: 59.3±8.1 years) fulfilling the 2010 ACR/EULAR classification criteria [105] were included as a control group. The control groups were matched in gender ratio to the SSc study group.

The subjects' written informed consent was obtained according to the Declaration of Helsinki (updated 2008). The study was approved by the Regional and Institutional Research Ethics Committee, Clinical Centre, University of Pécs (4906/2013) and the Hungarian National Ethics Committee (IF-6720-6/2015.).

#### 4.1.1.2. Multicentre study

The DeSScipher study ("to decipher the optimal management of systemic sclerosis" [106]) is a multinational, longitudinal study embedded in the EUSTAR database [107, 108].

From May 2013 until the end of November 2015 2162 patients with SSc were enrolled into the DeSScipher study. Adult patients fulfilling the ACR and/or the new ACR-EULAR SSc criteria were included into the "Arthritis group" (n=100), if showing signs of arthritis. Arthritis was defined as at least 2 swollen and tender joints on physical examination of the 28 joint count (wrists, elbows, shoulders, knees, MCP and PIP joints). In addition, the DIP joints were also assessed. Patients with no signs of inflammatory joint involvement, defined as having less than 2 tender and swollen joints on physical examination were included in the "Non-arthritis group" (n=1686). Patients with significant hand disability or joint pain caused by other diseases were excluded from the analysis.

Patients were recruited from 34 study sites (10 DeSScipher Study partners + 24 EUSTAR contributing centres) from 14 countries (9 sites from Germany, 6 from Italy, 3 from United Kingdom and Romania, 2 from Switzerland, France and Russia, and 1 from Hungary, Croatia, Serbia, Belgium, Turkey, Egypt and Spain).

The subjects' written informed consent was obtained according to the Declaration of Helsinki (updated in 2008). Ethical approval was obtained for each enrolled study site (approval numbers of the Hungarian study site were: 24952/2012/EKU; 428/PI/2012.)

#### 4.1.2. Statistical analysis

Clinical data of the "Arthritis" and "Non-arthritis" groups were compared by Fisher's exact test, Mann-Whitney U test, and independent sample T test depending on the type of each variable. Kolmogorov-Smirnov test was used to test for normal distribution of continuous variables. Comparison of joint involvement on left and right side was done by McNemar's test.

### 4.2. Cross-cultural adaptation and validation of the Hungarian version of the CHFS in SSc and RA

#### 4.2.1. Study groups

All together 95 individuals, including 40 patients with SSc, 34 patients with RA and 21 healthy individuals took part in this study from October 2011 to July 2012 at the Department of Rheumatology and Immunology of University of Pécs. Their basic demographic characteristics are depicted in Table 3.

**Table 3 Demographic characteristics of 40 patients with systemic sclerosis (SSc), 34 patients with rheumatoid arthritis (RA) and 21 healthy controls (HC)**

| Study group | SSc | | RA | HC |
|---|---|---|---|---|
| | lcSSc[a] | dcSSc[b] | | |
| **number of individuals** | 18 | 22 | 34 | 21 |
| **gender (females/males)** | 18/0 | 19/3 | 25/9 | 20/1 |
| **age (mean ± SD, years)** | 60.8 ± 13.6 | 55.8 ± 12.3 | 57.7 ± 12.5 | 58.6 ± 11.7 |

[a]*limited cutaneous SSc,* [b]*diffuse cutaneous SSc*

All participants were informed about the goals, methods and consequences of the study; and verified their voluntary participation by signing the consent-form. The study was approved by the Regional and Institutional Ethical Committee of the University of Pécs (2720/2006).

### 4.2.2. Assessments

The evaluation of patients included examining 28 joints and calculating the DAS28-ESR, the Finger to Palm distance (FTP) and Hand Anatomic Index (HAI) values. The following joints were tested for tenderness and swelling: MCPs, PIPs, wrist, elbows, shoulders and knees. In addition to the newly validated CHFS all participants filled out the previously validated HAQ-DI and the adjacent visual analogue scale measuring pain (Pain-VAS). CRP and ESR values were gathered from patient history. Only CRP and ESR measurements carried out within the month of the study visit were taken into account.

The CHFS was originally developed for rapid assessment of RA patients' hand, later it was also validated and successfully used for patients with SSc and with osteoarthritis [17, 43, 109-112]. The questionnaire consists of 18 questions concerning activities of daily living. The questions fall into 5 categories: dining, dressing, hygiene, office, and other activities. The questions can be also categorised according to what kind of hand movement they ask about. The three subgroups refer to activities requiring strength and rotational movement; fine motoric skills and dexterity; gripping strength and movement of the first, second and third fingers of dominant hand [109, 110]. The answers are given on a 6-point Likert scale from 0 to 5. Zero point refers to the best functional status of the hands, i.e. the patient can carry out

the task without any difficulty, while the worst state of function is scored with 5 points, which means the task in question is impossible for the patient. It takes 3-5 minutes to fill in the questionnaire. The final test score is the simple summation of the 18 scores given for each answer, the lowest possible score being 0 and the highest 90.

### 4.2.3. Adaptation

We performed the translation and adaptation to the Hungarian culture of the questionnaire according to the so called "forward-backward translation" method [113]. First two physicians and two non-informed (not health professional) English teachers translated the questionnaire from English to Hungarian. Than an expert group, including a physician, a medical student, a professional physical therapist, a linguist and two patients with SSc created the first Hungarian version of the questionnaire. This was then translated back to English by two independent non-informed individuals, with an English mother tongue, but who have been living in Hungary for a long time. On comparison of the original English and the test once again translated back to English there was no significant difference in their meaning. Then trial-tests were handed out to a group of patients with SSc, to ensure that the test was comprehensible. The patients did not suggest any changes, so the previous expert group finalised the Hungarian version of the CHFS.

### 4.2.4. Validation and statistical analysis

The CHFS was validated using the OMERACT filter [114-116], described in Table 4. Construct validity was assessed by analysing correlation of CHFS with previously validated similar tests, such as the HAQ-DI, Pain-VAS, HAI and Delta-FTP. Content validity was tested by checking for the presence of floor and ceiling effect. Regarding structural validity, the questions of CHFS were expected to fall into 2 or 3 principal components according to previous literature about validation of CHFS. Octagonal rotation was used in the principal component analysis. For analysing test-retest reliability, the patients were asked to fill in the CHFS twice within approximately a week time, assuming the patients' disease state did not change significantly over this short period of time. Intraclass correlation coefficient (ICC) was calculated using the tests from the two separate time points. We also examined weather the CHFS was able to discriminate between patient groups with different functional state: SSc versus (vs.) RA, lcSSc vs. dcSSc, severe vs mild hand damage measured by HAQ, HAI or

Delta-FTP. Internal consistency of the questionnaire was tested by calculating Cronbach's alpha. Significant increase of data consistency was not anticipated on alternating omission of one of the domains.

**Table 4 OMERACT filter: recommendations for outcome measure validation**

| OMERACT filter | |
|---|---|
| **Truth** | Face validity |
| | Construct validity |
| | Content validity |
| | Structural validity |
| **Discrimination** | Test-retest reliability |
| | Internal consistency |
| | Discriminant validity |
| | Responsiveness |
| **Feasibility** | Time |
| | Training |
| | Equipment |
| | Cost |

*OMERACT:* Outcome Measures for Rheumatoid Arthritis Clinical Trials

### 4.3. Validation of articular DAIs in SSc

#### 4.3.1. Study groups

In addition to the 77 patients with SSc and 40 patients with RA described in details previously (see section 4.1.1.1) 20 patients with primary Raynaud's phenomenon (RP) (mean age ± SD: 41±13.3 years) and 28 healthy volunteers (mean age ± SD: 51.0±15.6 years) were recruited as control groups. These groups were also matched in gender ratio to the SSc study group.

The subjects' written informed consent was obtained according to the Declaration of Helsinki (updated 2008). The study was approved by the Regional and Institutional Research Ethics Committee, Clinical Centre, University of Pécs (4906/2013) and the Hungarian National Ethics Committee (IF-6720-6/2015.).

### 4.3.2. Assessments

Articular disease activity was assessed using the DAS28-ESR, the DAS28-CRP, the CDAI and the SDAI. [6, 117-120]. DAS28-ESR is computed with a complicated formula from the 28 joint swelling count (28JSC), the 28 joint tenderness count (28JTC), patient's assessment of global health on a 100 mm visual analogue scale (VAS-GH), and the erythrocyte sedimentation rate (ESR) [6].

Since CRP is more sensitive to short-term changes of inflammation than ESR, and CRP was found to be associated with radiological progression in patients with RA, the DAS28-CRP was established by Fransen *et al* [120, 121]. DAS28-CRP is calculated with slight modification of the DAS28-ESR formula, using the same variables, except for using (CRP) level (in mg/dl) instead of ESR [117, 120].

SDAI is the numerical summation of the following variables: 28JTC, 28JSC, CRP (in mg/dl), patient's and physician's assessment of disease activity (in cm) on a 10 cm VAS (VAS-Patient and VAS-Physician) [119]. CDAI is the numerical summation of the same variables as SDAI, except for CRP [118].

The formula of the DAIs are described below followed by the range of values each DAI can take[122].

$$\text{DAS28-ESR}=(0.56*\sqrt{28\text{JTC}}+0.28*\sqrt{28\text{JSC}}+0.70*\ln(\text{ESR})+0.014*\text{VAS-GH}$$

(range: 0.49-9.08)

$$\text{DAS28-CRP}=0.56*\sqrt{28\text{JTC}}+0.28*\sqrt{28\text{JSC}}+0.36*\ln(\text{CRP}+1)+0.014*\text{VAS-GH}+0.96$$

(range: 1.21-8.48)

$$\text{SDAI}=28\text{JTC}+28\text{JSC}+\text{CRP}+\text{VAS-Patient}+\text{VAS-Physician} \quad \text{(range: 0.1-86.0)}$$

$$\text{CDAI}=28\text{JTC}+28\text{JSC}+\text{VAS-Patient}+\text{VAS-Physician} \quad \text{(range: 0-76)}$$

According to Koevoets *et al* [123], "Patients' assessment of global heath" VAS can be replaced by the "Patients' assessment of disease activity" VAS upon calculation of the DAS28-ESR used in patients with RA. Since SSc is a multimodal disease we calculated these indices for patients with SSc using the "physician's assessment of articular disease activity" VAS instead of using the "physician's assessment of global disease activity" VAS; and using

the “patient’s assessment of arthritis” VAS instead of the “patient’s assessment of global health” VAS.

Besides the 28 joint count assessments, the number of tender and swollen DIPs was also assessed in each group. The 8 joint counts concerning tenderness and swelling (8JTC and 8JSC, respectively) were calculated separately as described above.

Disease activity of SSc was assessed by the EscSG-AI and the MSAI. EscSG-AI composes of 5 domains (skin, vascular, lung-heart, joint, laboratory), which are weighted and added up into a total score of 0 to 10 [98]. MSAI was derived from the EscSG-AI with different weighting of the items and incorporating additional measures, i.e. patient’s reported skin score, HAQ-DI, and the value of FVC/DLCO [101].

Structural hand damage was examined by the HAI and the Delta Finger to Palm distance (delta-FTP). HAI is defined as the maximum hand spread minus the closed hand span divided by maximum lateral hand height [20]. Delta-FTP is calculated by extracting the FTP distance – measured between the tip of the middle finger and the palm during maximal finger flexion – from the distance measured between the same two points during maximal finger extension [22]. The number of joint contractures was assessed in the joints of the 28 joint count (CoC28). Contracture was defined as present in a joint in case of at least 25% decrease in range of motion in at least one joint-movement direction [124].

All participants filled out a set of fully validated questionnaires on hand function, global function, and quality of life [2, 23]. HAQ-DI assesses the functionality of patients using 20 multiple-choice questions regarding activities of daily living [18]. CHFS is similar to HAQ-DI; however it only refers to the hands [8]. The Quick Questionnaire of the Disability of the Hands, Arms, and Shoulders (qDASH) measures disability of the upper extremities; it was validated to SSc by our research group [23]. The Scleroderma Health Assessment Questionnaire (SHAQ) – in addition to the HAQ-DI – contains also 5 VASs measuring the effect of lung and gastrointestinal involvement, digital ulcers, Raynaud’s phenomenon and overall disease on the patient’s life [19]. The 36-Item Short Form Health Survey (SF36) assesses health related quality of life on two scales: the Mental Component Summary (MCS) and the Physical Component Summary (PCS) [125].

### 4.3.3. Validation

The OMERACT filter was used to assess the validity of the DAIs including feasibility, truth, and discrimination. This methodology was developed for validation of test used for rheumatic diseases [114-116]. Construct validity was assessed by calculating the correlation between the particular articular indices and other instruments reflecting disease activity, joint involvement, and hand function. Content validity was assessed by principal component analysis of outcomes measures of disease activity and damage, and by looking for floor and ceiling effects. Floor and ceiling effects were considered present if more than 15% of respondents achieve the highest or lowest possible score. The minimum and maximum value of DAS28-ESR, DAS28-CRP and SDAI depend on the lowest and highest possible value of ESR and CRP, which were considered to be 2 and 100 mm/h in case of ESR, whereas ≤ 0.1 mg/dl and 10 mg/dl in case of CRP according to the literature [122]. Structural validity was assessed by testing unidimensionality of the DAIs with principal component analysis.

For testing interobserver reliability, two raters, an experienced rheumatologist (GK) and a young physician (VL) examined a subgroup of patients with SSc (n=20) independently from each other. For testing intraobserver reliability, a subgroup of patients (n=12) was assessed by the same observer twice within five days assuming disease activity did not change within this period of time. The articular disease activity of the patients was considered stable during this interval. Discrimination was examined between the SSc and the control groups, then on SSc subgroups based on various characteristics: cutaneous subset, disease duration (≤4 years and >4 years), MRSS (≤14 and >14), EscSG-AI (≤3 and >3) [98], HAQ-DI (<1 and ≥1)[126], CRP (≤5 mg/l and >5), ESR (≤30 and >30 mm/h), HAI ((≤2 and >2)[20, 23].

### 4.3.4. Statistical analysis

Spearman's rank correlation test was used to determine construct validity. Intra- and interobserver reliability was assessed by ICC and Cronbach's alpha. Data regarding continuous variables are shown as mean ± standard deviation or median, upper or lower quartiles, depending on normal distribution of the varibles. Discrimination between subgroups was tested by Mann-Whitney U test for continuous variables and with $\chi 2$-test for categorical variables. Principal component analysis was used to test content and structural validity. SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses.

# 5. RESULTS

## 5.1. Investigation of distribution of joint involvement in SSc

### 5.1.1. Single centre study

The clinical characteristics of our SSc cohort (67 females/10 males, age 56.3±11.8, years, disease duration: 10.5±9.5 years) are described in Table 5. In the RA cohort (36 females/4 males, age: 59.3±8.1 years, disease duration: 15.2±9.1) 26 patients were RF positive, and 24 were anti-CCP positive, while in the SSc cohort 18 patients were RF positive and one was anti-CCP positive.

**Table 5 Clinical characteristics of the 77 patients with systemic sclerosis (SSc)**

| Clinical characteristics | SSc (n=77) |
|---|---|
| Diffuse / Limited cutaneous subset | 50/27 (65%/35%) |
| Anticentromere antibody positive | 21 (27%) |
| Anti-topoisomerase I antibody positive | 32 (42%) |
| Modified Rodnan Skin Score | 15 (9; 22) |
| Lung fibrosis on HRCT | 55 (71%) |
| FVC<70% predicted[a] | 8 (10%) |
| DLCO<70% predicted[b] | 47 (61%) |
| Pulmonary artery hypertension[c] | 3 (4%) |
| Diastolic dysfunction[d] (n=72) | 36 (47%) |
| Scleroderma renal crisis | 1 (1%) |
| Digital ulcer | 15 (19%) |
| Subcutaneous calcinosis on the hands | 8 (10%) |
| Contracture[e] | 43 (56%) |
| Tendon friction rubs | 19 (25%) |
| EscSG-AI[f] | 1.5 (0.5; 2.0) |
| Modified Scleroderma Disease Activity Index | 1.5 (1.0; 2.5) |
| Rheumatoid arthritis (RA) overlap[g] | 3 (4%) |

*Variables are indicated as median (quartiles) or number of patients (percentage) as required. Abbreviations: [a]forced vital capacity, [b]diffusing capacity of the lung for carbon monoxide, [c]defined as right heart pressure greater than 40 mmHg by right heart catheterization, [d]defined by transthoracic echocardiography, [e]defined as at least 25% decrease in range of motion in at least one joint-movement direction, examined in the 28 joint count, [f]European Scleroderma Study Group Activity Index, [g]according to the 2010 ACR/EULAR RA classification criteria.[105]*

Number of swollen and tender joints in the SSc and RA cohorts is described in Table 6. There was not any tender joint in half of the patients with SSc; which meant a significantly higher rate of patients, than in the RA cohort (p=0.007). Meanwhile there was no statistically significant difference regarding the rate of patients with zero, one to five and more than five swollen joints in the SSc and RA cohorts (p=0.061).

**Table 6 Number of affected joints in 77 patients with systemic sclerosis (SSc) and 40 patients with rheumatoid arthritis (RA)**

| Symptom | Number of affected joints out of 28 joints | SSc (n=77) | RA (n=40) | Statistical comparison (p-value) |
|---|---|---|---|---|
| Joint tenderness | 0 | 40 (52%) | 9 (22.5%) | .007 |
| | 1-5 | 15 (19%) | 15 (37.5%) | |
| | 6 or more | 22 (29%) | 16 (40%) | |
| Joint swelling | 0 | 52 (68%) | 18 (45%) | .061 |
| | 1-5 | 21 (27%) | 18 (45%) | |
| | 6 or more | 4 (5%) | 4 (10%) | |

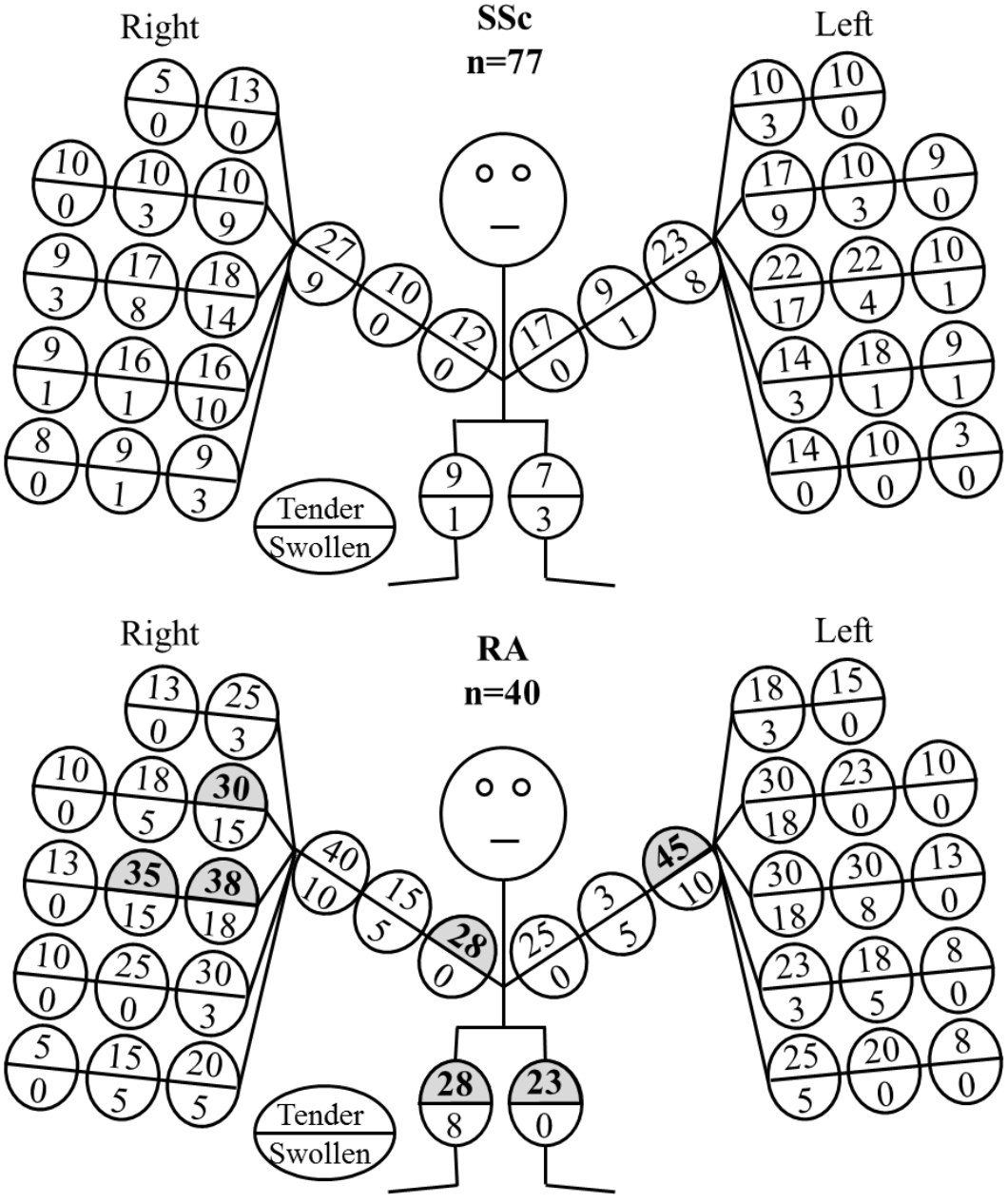
*Rate of patients with 0, 1 to 5 and more than 5 affected joints in the SSc and RA cohort was compared by $\chi^{2}$-test.*

The prevalence of tenderness and swelling in each joint regarding the SSc and RA cohorts is depicted in Figure 1. In the SSc cohort, the wrists, the MCPs and the PIPs were most often affected; while knee, elbow and DIP involvement was much less frequent. Distribution of joint swelling and tenderness was similar to each other in the SSc cohort. However, in patients with SSc joint tenderness was significantly more frequent ($p<0.05$) than swelling in most of the investigated joints (wrists, elbows, shoulders, PIPs). Swelling was particularly rare in the large joints of the patients with SSc. Among the fingers, the second and third fingers were the most often affected in the SSc cohort. The prevalence of swelling was significantly higher in the right MCP joint than in the left in the SSc cohort (p=0.031). No other statistically significant difference was found on comparison of left and right side involvement of the patients with SSc.

Distribution of both, joint tenderness and joint swelling was similar in the SSc and the RA cohort. However, tenderness was statistically more frequent in the right third PIP, the right second and third MCPs, the right shoulder, left wrist and in both knee joints of the patients with RA compared to the patients with SSc ($p<0.05$). (See bold characters of Figure 1).

There was no significant difference in the number of tender DIPs and the number of swollen DIPs between patients with RA and SSc. No statistically significant difference was found regarding left and right side involvement in the patients with RA.

**Figure 1 Prevalence of tenderness and swelling of each joint in the 77 patients with systemic sclerosis (SSc) and 40 patients with rheumatoid arthritis (RA)**




*Bold characters represent significantly higher percentages comparing patients with SSc to patients with RA by χ2 test or Fisher's exact test as required.*

### 5.1.2. Multicentre study

The comparison of demographic and clinical characteristics of the "Arthritis group" and the "Non-arthritis group" are depicted in Table 7.

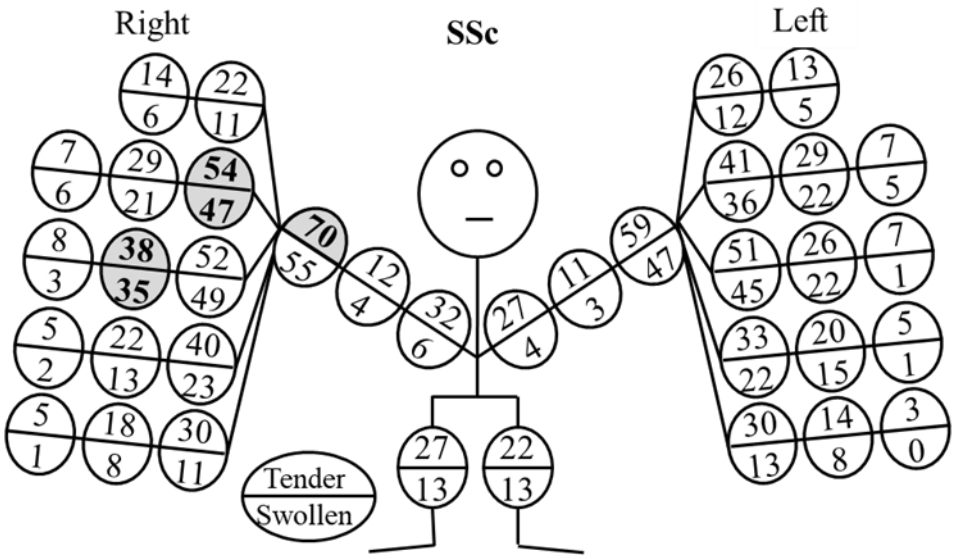
Patients with arthritis had a higher rate of female gender, higher frequency of muscle involvement and higher prevalence of decreased DLCO compared to patients without signs of arthritis. All further analyses were done using data of the "Arthritis group".

**Table 7 Demographic and clinical characteristics of the 1786 patients with systemic sclerosis (SSc) included in the multicentre study**

| Patient characteristics | Arthritis group n=100 | Non-arthritis group n=1686 | Comparison of groups |
|---|---|---|---|
| Age | 59.8±13.9 | 57.2±13.0 | 0.050 |
| Disease duration (years) | 8.4 (4.4; 16.4) | 9.2 (4.6; 15.2) | 0.958 |
| Female | 94 (94%) | 1418 (84%) | 0.006 |
| Diffuse cutaneous subset | 31 (33%) | 523 (34%) | 0.911 |
| MRSS in dcSSc[a] (n=554) | 14 (10; 19) | 11 (5;17) | 0.043 |
| Antitopoisomerase antibody | 23 (43%) | 385 (39%) | 0.568 |
| Anticentromere antibody | 25 (43%) | 356 (36%) | 0.326 |
| Lung fibrosis on HRCT[b] | 48 (62%) | 779 (60%) | 0.905 |
| FVC <70% predicted[c] | 6 (9%) | 158 (14%) | 0.356 |
| DLCO<70% predicted[d] | 46 (75%) | 650 (60%) | 0.015 |
| Pulmonary hypertension by RHC[e] | 5 (5%) | 93 (6%) | 1.000 |
| Scleroderma renal crisis | 0 (0%) | 25 (2%) | 0.395 |
| Muscle involvement[f] | 28 (29%) | 305 (19%) | 0.025 |
| ESR (mm/h) | 18 (10; 32) | 16 (8; 28) | 0.115 |
| CRP (mg/l) | 3.0 (1.1; 9.0) | 2.4 (1.0; 5.5) | 0.090 |
| EscSG-AI >3[g][98] | 20 (20%) | 161 (10%) | 0.003 |
| HAQ-DI[h] | 1.4 (0.9; 2.0) | 0.8 (0.1; 1.5) | 0.000 |

*Variables are indicated as mean ± standard deviation, median (quartiles) or number of patients (percentage) as required. Patient groups were compared by Fisher's exact test, Mann-Whitney U test, and independent sample T test as required. Abbreviations: [a]modified Rodnan skin score in patients with diffuse cutaneous SSc, [b]high resolution computer tomography, [c]forced vital capacity, [d]diffusing capacity of the lung for carbon monoxide, [e]right heart catheterisation, [f]muscle weakness and/or muscle atrophy on physical examination, [g]European Scleroderma Study Group Activity Index, [h]Health Assessment Questionnaire Disability Index*

**Figure 2 Prevalence of tenderness and swelling in each joint in 100 patients with systemic sclerosis (SSc)**

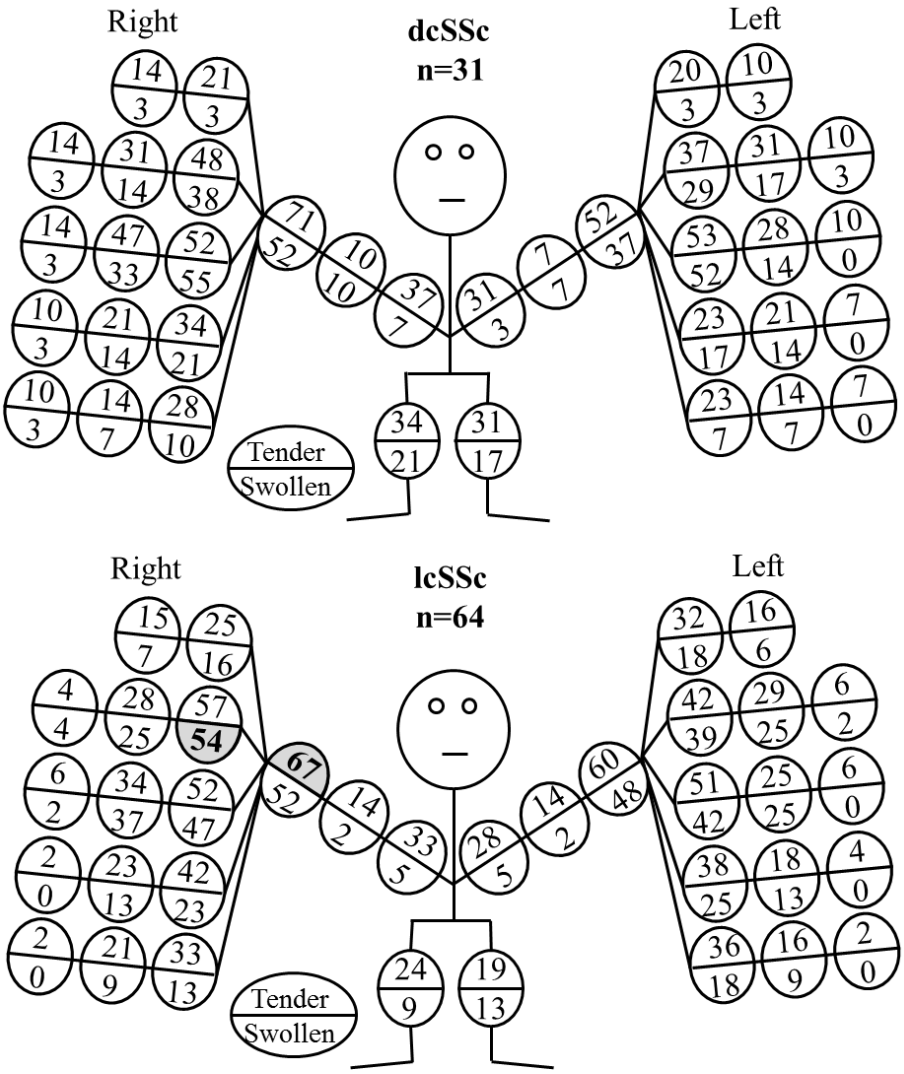



*Bold characters represent significantly higher percentages compared to the other side of the patients by McNemar's test.*

Distribution of joint tenderness was similar to distribution of swelling in the examined SSc patients. The wrists, the second, and the third MCP joints were most often tender and most frequently swollen (Figure 2). The first MCP joints were significantly more often swollen in patients with lcSSc (22%) than in patients with dcSSc (3%) (p=0.029), while there were no significant differences regarding any other joints. No significant difference was found regarding involvement of each joint comparing anti-topoisomerase I antibody positive and anti-centromere antibody positive patients. There was also no significant difference on comparison of early (i.e. disease duration < 3 years) and late cases (i.e. disease duration ≥ 3 years). (data not shown)

There was no significant difference between the left and right side of patients with dcSSc regarding the frequency of the involvement of each joint. Meanwhile tenderness of the wrist and swelling of the second MCP joint was significantly more frequent on the right side of patients with lcSSc, than on the left (Figure 3).

**Figure 3 Prevalence of tenderness and swelling of each examined joint in 31 patients with diffuse (dcSSc) and 64 patients with limited cutaneous systemic sclerosis (lcSSc)**




*Bold characters represent significantly higher percentages compared to the other side of the patients by McNemar's test.*

### 5.2. Cross-cultural adaptation and validation of the Hungarian version of the CHFS in SSc and RA

Patients filled in the CHFS in 2 minutes and 40 seconds on average. The study participants' test results and inflammatory parameters are assessed in Table 8.

**Table 8 Test results of 40 patients with systemic sclerosis (SSc), 34 patients with rheumatoid arthritis (RA) and 21 healthy controls (HC)**

| Tests (range) | HC n=21 | RA n= 34 | SSc n=40 | lcSSc[a] n=18 | dcSSc[b] n=22 |
|---|---|---|---|---|---|
| **CHFS[c] (0-90)** | 5 (1.0; 8.0) | 19**(8.3; 36.3) | 14*(3; 26.8) | 7 (2.5; 24.5) | 15.5**(4.5; 31) |
| **HAQ-DI[d](0-3)** | 0.25 (0; 0.5) | 1.5**(0.9; 2.1) | 1.3**(0.7; 1.8) | 1.1*(0.25; 1.9) | 1.5**(0.7; 1.75) |
| **Pain-VAS[e]** | 15 (3; 28) | 50**(27.5; 75) | 34**(20; 57) | 42.5*(14; 62) | 30*(20; 53) |
| **DAS28-ESR[f]** | - | 4.14 (3.0; 5.7) | 3.4 ( 2.5; 4.3) | 3.5 ( 2.7; 5.4) | 3.2 ( 2.4; 3.6) |
| **HAI[g] (right)** | - | 2.1 (1.3; 2.6) | 1.8 (1.3; 2.3) | 1.95 (1.4; 2.3) | 1.55 (1.3; 2.4) |
| **Delta-FTP[h]** | - | - | 7.0 ( 5.2; 8.9) | 7.9 ( 6.4; 9.6) | 6.35 ( 4.2; 8.8) |
| **ESR (mm/h)** | - | 21.5 ± 18.9 | 22.6 ± 18.8 | 29.7 ± 24.2 | 16.9 ± 10.3 |
| **CRP[i] (mg/l)** | - | - | 5.4 ± 5.8 | 7.1 ± 6.6 | 3.9 ± 4.7 |

*Values are depicted as median (quartiles) or mean ± standard deviation as required. Patient cohorts were compared to the HC group by Mann-Whitney U tests. *p<0.05, **p<0.01 Abbreviations: [a]limited cutaneous SSc, [b]diffuse cutaneous SSc, [c]Cochin Hand Function Scale, [d]Health Assessment Questionnaire Disability Index, [e]100 mm visual analogue scale measuring pain. [f]Disease Activity Score of 28 joints using erythrocyte sedimentation rate, [g]Hand Anatomic Index, [h]Delta Finger to Palm distance, , [i]C-reactive protein.*

### 5.2.1. Construct validity

Spearman's rank correlation analysis showed significant correlation between CHFS, HAQ-DI and tests referring to structural hand damage – such as HAI and Delta-FTP – in patients with SSc and also in patients with RA.

Moreover, significant correlation was found between CHFS and the DAS28-ESR measuring articular disease activity, but there was not any correlation between CHFS and CRP, as well as CHFS and ESR (Table 9).

### 5.2.2. Content validity

On examination of the floor and ceiling effect, the best possible functional status measured by the CHFS (0 points) was reached by 5 patients with SSc (13%) and by 4 patients with RA (12%). The maximum score of the test (90 points), meaning the worst possible hand function was not reached by any of the patients.

**Table 9 Spearman's correlation analysis of the Cochin Hand Function Scale (CHFS) and other tests in 40 patients with systemic sclerosis (SSc) and 34 patients with rheumatoid arthritis (RA)**

| Spearman's correlation | **SSc n=40 CHFS** | **RA n=34 CHFS** |
|---|---|---|
| **Age** | NS[a] | 0.400[*] |
| **HAQ-DI**[b] | 0.709[***] | 0.831[***] |
| **DAS28-ESR**[c] | 0.454[**] | 0.471[**] |
| **HAI**[d] **(right hand)** | - 0.512[**] | - 0.376[*] |
| **Delta-FTP**[e] **(right hand)** | - 0.649[***] | ND[f] |
| **Pain-VAS**[g] | 0.624[***] | 0.365[*] |
| **ESR** | NS | NS |
| **CRP** | NS | ND |

*[*]p<0.05, [**]p<0.01 [***]p<0.001, Abbreviations: [a]not significant, [b]Health Assessment Questionnaire Disability Index, [c]Disease Activity Score of 28 joints using erythrocyte sedimentation rate, [d]Hand Anatomic Index, [e]delta Finger to Palm distance, [f]no data, [g]100 mm long visual analogue scale measuring pain*

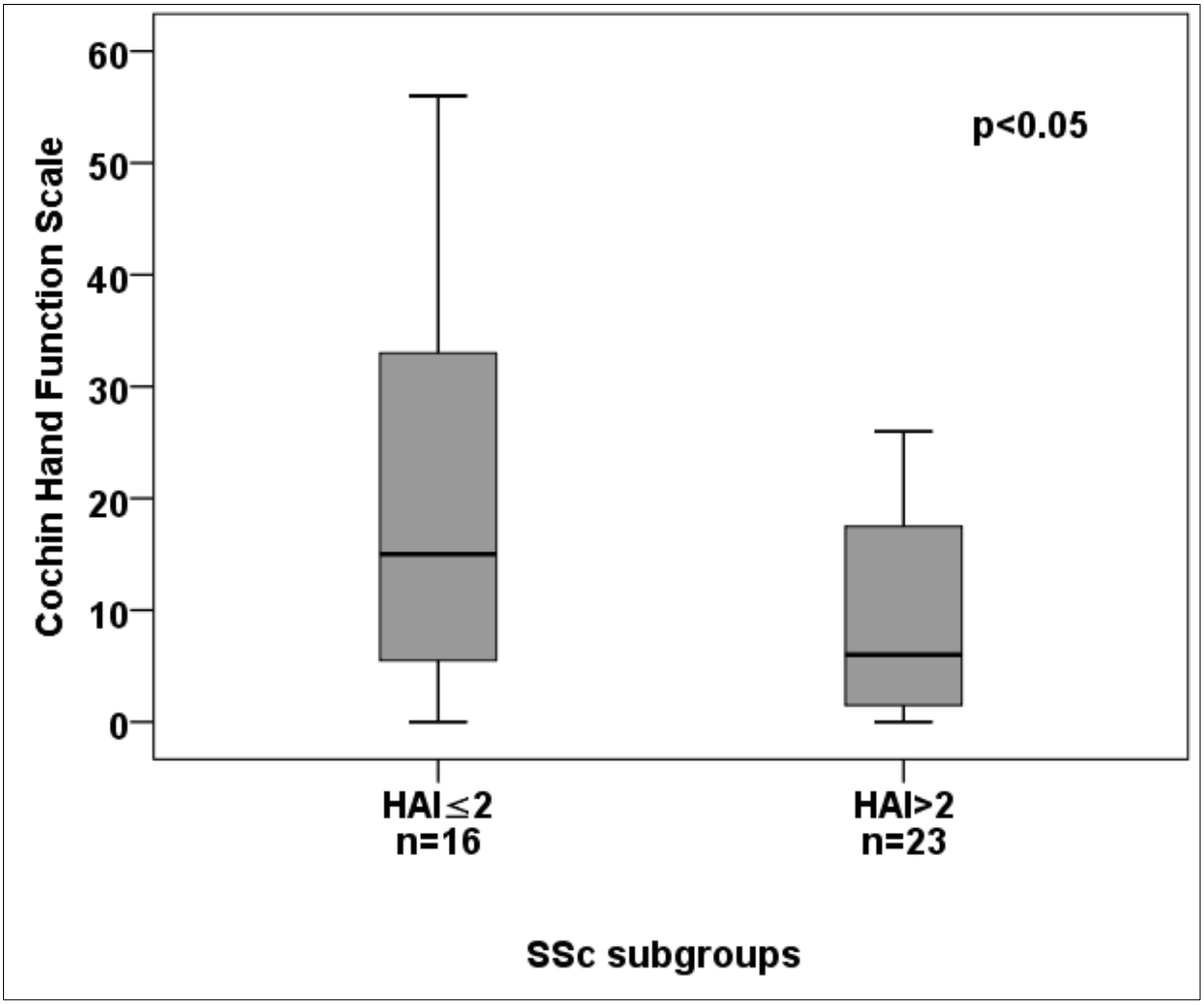
### 5.2.3. Structural validity

The questions were combined into two main components by the principal component analysis. The first dimension comprised of questions referring to activities requiring strength and rotational hand movements (question 1, 2, 3, 4, 7, 9, 10, 11, 12, 15, and 18), while the other contained questions concerning dexterity and fine motoric skills (question 5, 6, 8, 13, 14, 16, and 17).

### 5.2.4. Discriminative validity

There was a significant difference regarding the CHFS and the pain-VAS values of the SSc and the healthy control group ($p < 0.05$), and also between the RA and the healthy control group ($p<0.001$). However, there was no significant difference between the SSc and the RA group regarding CHFS, HAQ-DI, pain-VAS, DAS28-ESR and HAI.

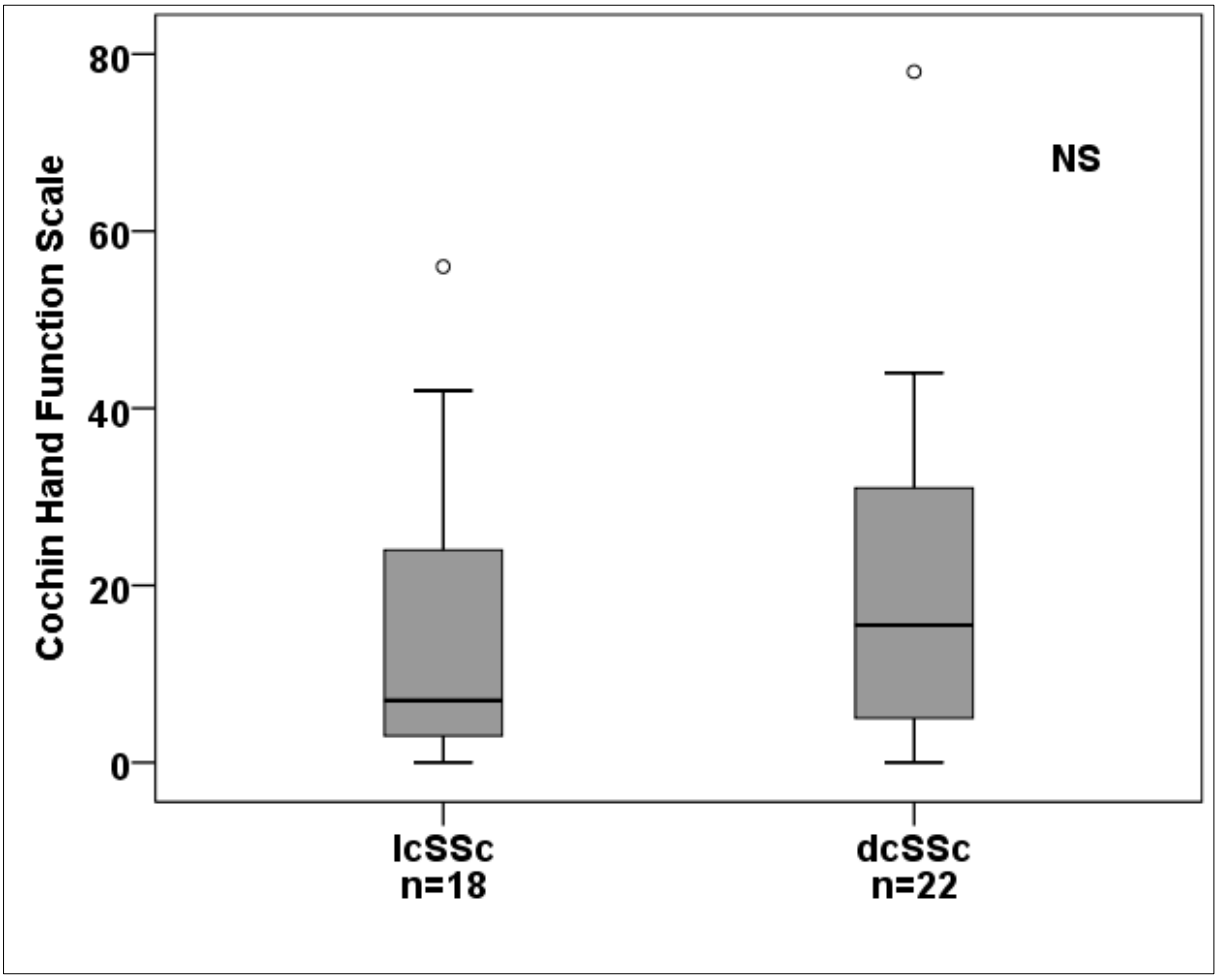
**Figure 4 Comparison of Cochin Hand Function Scale (CHFS) values of 16 systemic sclerosis (SSc) patients with and 23 without severe structural hand damage determined by the Hand Anatomic Index (HAI)**




*Statistical comparison was done by Mann-Whitney U test.*

We also compared SSc patients with severe hand damage measured by HAI and Delta-FTP to SSc patients with milder hand damage (HAI≤2 vs. HAI >2; Delta-FTP<7cm vs. Delta-FTP >7cm). We found statistically significant difference between the CHFS scores of these two groups by Mann-Whitney U test (Figure 4). However, there was no significant difference between the patients with lcSSc and dcSSc regarding hand function measured by CHFS (Figure 5).

**Figure 5 Comparison of Cochin Hand Function Scale values of 18 limited cutaneous (lcSSc) and 22 diffuse cutaneous systemic sclerosis (dcSSc) patients**



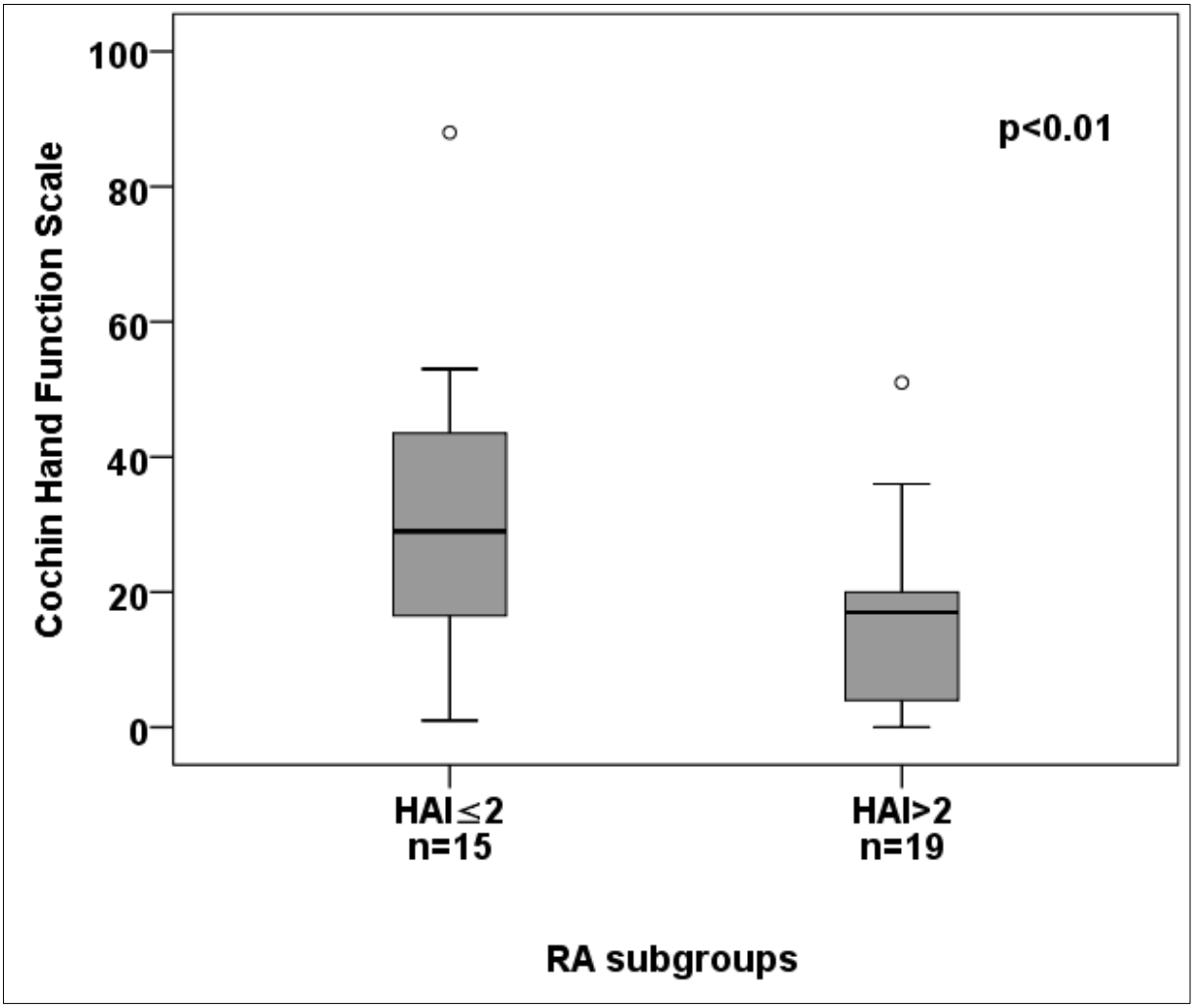

*NS: No significant difference was found between the subgroups by Mann-Whitney U test.*

There was also significant difference regarding CHFS scores between patients with RA divided based on reduction of hand mobility measured by HAI (Figure 6). In cases of HAI values less than 2 severe hand joint contractures can be observed; these patients had also higher CHFS scores.

### 5.2.5. Reliability: internal consistency and reproducibility

Internal consistency of the questionnaire was assessed by calculation of the Cronbach's alpha, which was found to by high, 0.975. The CHFS tests filled out by patients with SSc and RA 5 to 7 days after their first test showed high ICC (0.96) with the baseline CHFS values ($p<0.001$).

**Figure 6 Comparison of Cochin Hand Function Scale values of 15 rheumatoid arthiritis (RA) patients with and 19 without severe structural hand damage determined by the Hand Anatomic Index (HAI)**




*Statistical comparison was done by Mann-Whitney U test.*

### 5.3. Validation of articular DAIs in SSc

The main clinical manifestations of the investigated SSc cohort have been described previously in Table 5. (See section 5.1.1.) Clinical data and results of outcome measures regarding the four study groups are depicted in Table 10. No significant difference was found in the composite indices in SSc patients with a disease duration ≤4 years vs. >4 years.

**Table 10 Demographic data and test results of 77 patients with systemic sclerosis (SSc), 40 patients with rheumatoid arthritis (RA), 20 patients with primary Raynaud's syndrome (PR) and 28 healthy controls (HC)**

| | Study groups | | | | Statistical comparison | | |
|---|---|---|---|---|---|---|---|
| | **SSc n=77** | **RA n=40** | **PR n=20** | **HC n=28** | **RA vs.[a] SSc** | **PR vs. SSc** | **HC vs. SSc** |
| **Gender (F/M)** [b] | 67/10 (87/13) | 36/4 (90/10) | 18/2 (90/10) | 25/3 (89/11) | 0.637 | 0.718 | 0.755 |
| **Age** | 56.3±11.8 | 59.3±8.1 | 38.7±13.5 | 51±15.6 | 0.106 | 0.000 | 0.012 |
| **Disease duration** [c] | 10.5±9.5 | 15.2±9.1 | 10.5±9.6 | NA[d] | 0.013 | 0.999 | NA |
| **RF**[e] | 18 (33%) n=54 | 26 (65%) | 2 (10%) | ND[f] | 0.002 | 0.045 | NA |
| **Anti-CCP**[g] | 1 (2%) n=50 | 24 (60%) | (0%) n=16 | ND | 0.000 | 0.569 | NA |
| **DAS28-ESR**[h] | 2.7 (2.0; 3.9) | 3.6 (2.8; 4.7) | 1.6 (1.3; 2.0) | 1.7 (1.4; 2.0) | 0.002 | 0.001 | <0.001 |
| **DAS28-CRP**[i] | 2.1 (1.5; 3.4) | 3.4 (2.4; 4.0) | 1.6 (1.3; 1.9) | 1.3 (1.1; 1.8) | 0.001 | 0.012 | <0.001 |
| **SDAI**[j] | 4 (1; 15) | 12 (4; 22) | 1 (0; 5) | 0 (0; 1) | 0.005 | 0.008 | <0.001 |
| **CDAI**[k] | 4 (1; 15) | 11 (4; 22) | 1 (0; 5) | 0 (0; 1) | 0.005 | 0.013 | <0.001 |
| **CRP (mg/l)** | 2.2 (1.3; 4.0) | 3 (1.7; 5.0) | 0.5 (0.3; 1.1) | 0.8 (0.5; 2.3) | 0.326 | <0.001 | 0.011 |
| **ESR (mm/h)** | 15 (8; 26) | 18 (9; 24) | 6 (4; 10) | 8 (6; 14) | 0.852 | <0.001 | 0.001 |
| **HAQ-DI**[l] | 0.88 (0.1; 1.4) | 1.31 (0.9; 1.8) | 0.0 (0.0; 0.8) | 0.0 (0.0; 0.0) | 0.007 | 0.001 | <0.001 |
| **QDASH**[m] | 32 (14; 48) | 42 (26; 59) | 8 (5; 23) | 0 (0; 6) | 0.023 | 0.003 | <0.001 |
| **CHFS**[n] | 7 (2; 19) | 12 (3; 24) | 1 (0; 6) | 0 (0; 0) | 0.396 | 0.002 | <0.001 |
| **HAI**[o] | 2.8 (2.2; 3.4) | 3.0 (2.6; 3.7) | 3.9 (3.4; 4.6) | 4.1 (3.5; 4.4) | 0.16 | <0.001 | <0.001 |
| **FTP**[p] | 19 (11; 27) | 14 (8; 21) | 0 (0; 6) | 0 (0; 7) | 0.041 | <0.001 | <0.001 |
| **Delta-FTP** | 76 (65; 87) | 76 (68; 86) | 92 (87; 96) | 94 (89; 100) | 0.97 | <0.001 | <0.001 |
| **SF36 PCS**[q] | 37 (29; 46) | 34 (27; 39) | 50 (37; 57) | 56 (50; 58) | 0.071 | 0.001 | <0.001 |
| **SF36 MCS** | 49 (37; 59) | 46 (29; 59) | 38 (26; 54) | 57 (52; 59) | 0.258 | 0.014 | 0.105 |
| **8JTC**[r] | 0 (0;3) | 2 (0;5) | 0 (0;1) | 0 (0;0) | 0.005 | 0.135 | 0.001 |
| **8JSC** | 0 (0;1) | 1 (0;2) | 0 (0;0) | 0 (0;0) | 0.040 | 0.004 | 0.001 |

*Values are indicated as median (quartiles), number (percentage) or mean ± standard deviation as required. The SSc cohort was compared to the control groups by Mann-Whitney U test or $\chi^2$-test as required. Abbreviations: [a]versus, [b]famales/males, [c]years since first non-Raynaud's symptom for patients with SSc, [d]not applicable, [e]rheumatoid factor, [f]not done, [g]anti-cyclic citrulinated peptide, [h]Disease Activity Score of 28 Joints using erythrocyte sedimentation rate, [i]Disease Activity Score of 28 Joints using C-reactive protein, [j]Simplified Disease Activity Index, [k]Clinical Disease Activity Index, [l]Health Assessment Questionnaire Disability Index, [m]Quick Questionnaire of the Disability of the Hands, Arms and Shoulders, [n]Cochin Hand Function Scale, [o]Hand Anatomic Index, [p]Finger to Palm distance, [q]36-Item Short Form Health Survey – Physical Component Summary and Mental Component Summary, [r]8 joint tenderness count and 8 joint swelling count*

### 5.3.1. Construct validity

DAS28-ESR, DAS28-CRP, and SDAI showed a significant correlation with disease activity measured by the EScSG-AI and the MSAI (Table 11).

**Table 11 Correlations of disease activity indices with functional status and disease activity measures in 77 patients with systemic sclerosis (SSc)**

| SSc n=77 | DAS28 -ESR[a] | DAS28 -CRP[b] | SDAI[c] | CDAI[d] | 8JTC[e] | 8JSC[f] |
|---|---|---|---|---|---|---|
| **DAS28-ESR** | - | .930*** | .889*** | .878*** | .845** | .686** |
| **DAS28-CRP** | .930*** | - | .952*** | .934*** | .850** | .718** |
| **SDAI** | .889*** | .952*** | - | .995*** | .812** | .716** |
| **CDAI** | .878*** | .934*** | .995*** | - | .814** | .717** |
| **MSAI[g]** | .402*** | .356** | .366** | .363** | .225* | .314** |
| **EScSG-AI[h]** | .344** | .337** | .355** | .345** | .255* | .317** |
| **CRP** | .299** | - | - | .201 | .079 | .117 |
| **ESR** | - | .253* | .181 | .151 | .093 | .137 |
| **VAS-physician[i]** | .701*** | .749*** | - | - | .738** | .673** |
| **HAQ-DI[j]** | .495*** | .485*** | .477*** | .486*** | .344** | .278* |
| **CHFS[k]** | .422*** | .350** | .344** | .356** | .243* | .200 |
| **QDASH[l]** | .617*** | .595*** | .589*** | .599*** | .492** | .303** |
| **VAS-overall (sHAQ[m])** | .469*** | .458*** | .492*** | .503*** | .338** | .308** |
| **VAS-Raynaud (sHAQ)** | .330** | .336** | .354** | .365** | .252* | .309** |
| **VAS-pain (HAQ)** | .515*** | .526*** | .548*** | .562*** | .400** | .313** |
| **VAS-joint pain** | .640*** | .680*** | .711*** | .716*** | .484** | .467** |
| **VAS-fatigue** | .476*** | .456*** | .488*** | .502*** | .354** | .312** |
| **SF36 PCS[n]** | -.578*** | -.565*** | -.568*** | -.583*** | -.437** | -.351** |
| **SF36 MCS** | -.192 | -.193 | -.255* | -.243* | -.126 | -.090 |

*Spearman's rank correlation coefficients are displayed in the table.* *$p<0.05$, **$p<0.01$, ***$p<0.001$, *Abbreviations:* [a]*Disease Activity Score of 28 Joints using erythrocyte sedimentation rate,* [b]*Disease Activity Score of 28 Joints using C-reactive protein,* [c]*Simplified Disease Activity Index,* [d]*Clinical Disease Activity Index,* [e]*8 Joint Tenderness Count,* [f]*8 Joint Swelling Count,* [g]*Modified Scleroderma Activity Index,* [h]*European Scleroderma Study Group Activity Index,* [i]*physician's assessment of articular disease activity on a visual analogue scale;* [j]*Health Assessment Questionnaire Disability Index,* [k]*Cochin Hand Function Scale,* [l]*Quick Questionnaire of the Disability of the Hands, Arms and Shoulders,* [m]*Scleroderma Health Assessment Questionnaire,* [n]*36-Item Short Form Health Survey Physical Component Summary and Mental Component Summary*

High correlation was observed between articular disease activity assessed by the physician on a VAS and DAS28-ESR as well as DAS28-CRP (Table 11).

The articular activity indices showed a strong correlation with measures of disability (HAQ, CHFS, qDASH, VAS-overall) (Table 11). SF36 PCS showed a significant (negative) correlation with all four articular DAIs, while SF36 MCS showed only weak (negative) correlation with SDAI and CDAI, and no correlation with DAS28-ESR and DAS28-CRP (Table 11). There was no correlation between the articular indices and the following parameters: age, disease duration, MRSS, HAI, Delta-FTP, CoC28 (data not shown).

### 5.3.2. Content validity

3.9%, 10.4%, 2.6% and 6.5% of the 77 patients with SSc achieved the lowest possible score regarding DAS28-ESR, DAS28-CRP, SDAI and CDAI respectively, while none of the patients reached the highest value regarding any of the four measures.

When loading measures corresponding to disease activity (CRP, ESR, MSAI, EScSG-AI, MRSS, HAQ, VAS-fatigue), measures of joint involvement (CHFS, qDASH, joint pain), measures of quality of life (SF36 PCS, SF36 MCS), measures of structural joint damage (HAI, Delta-FTP, CoC28) and the investigated DAIs into a principal component analysis, 55% of the original information was summarized into the first 2 components. All four DAIs as well as MSAI, HAQ, VAS-fatigue, CHFS, qDASH, joint pain and SF36 PCS fell into the first component; whereas measures of structural damage (HAI, Delta-FTP, CoC28) fell into the second component.

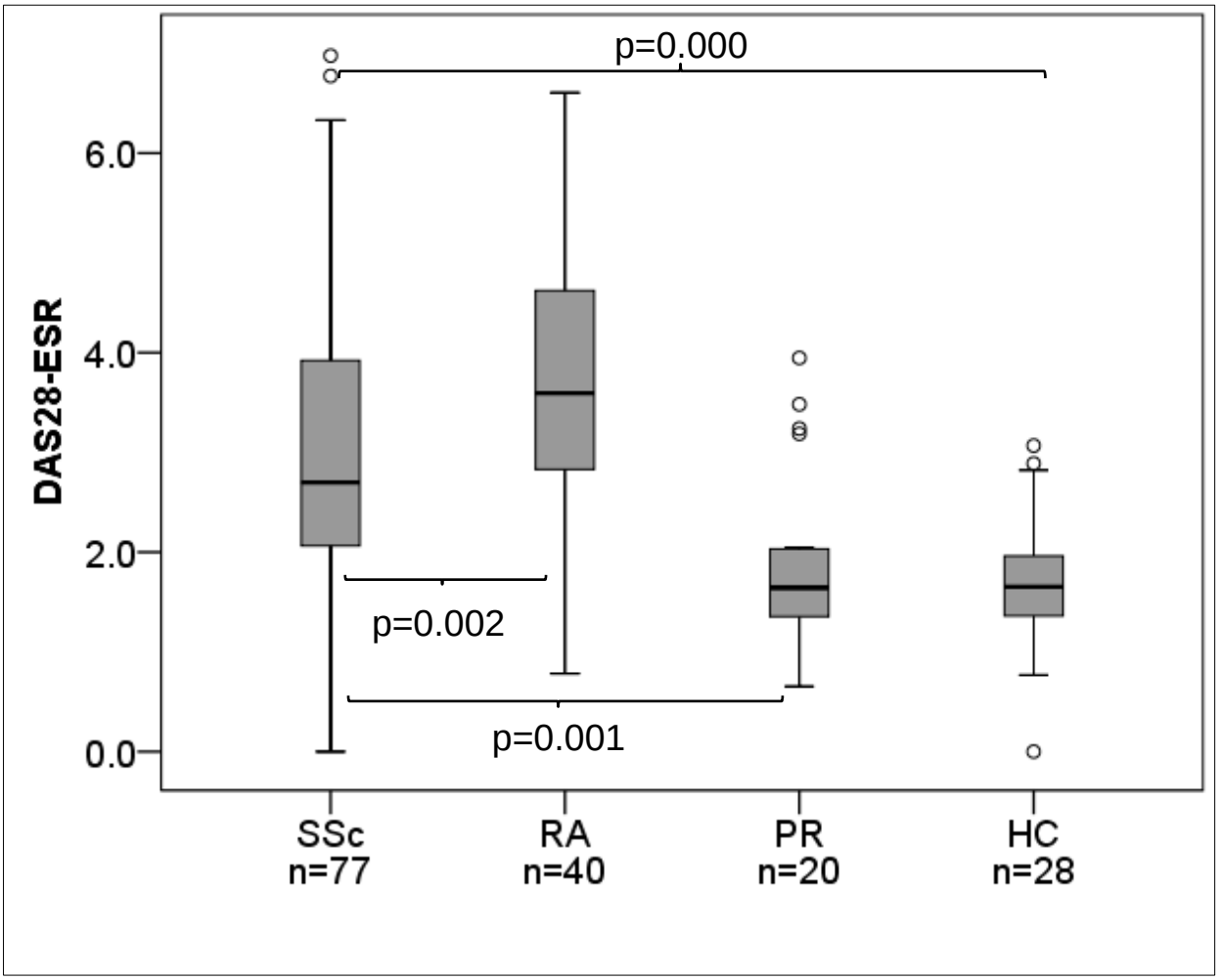
### 5.3.3. Structural validity

Principal component analysis was performed to check unidimensionality of the articular DAIs. The components were analysed as they are weighted in each index. All four indices were unidimensional, their components were grouped into a single factor, which explained 55.9%, 56.8%, 61.3%, and 71.8% of the variance for DAS28-ESR, DAS28-CRP, SDAI and CDAI, respectively.

### 5.3.4. Discriminant validity

Significant differences were seen in these particular composite indices comparing patients with SSc and patients with RA, PR and healthy controls (Figure 7).

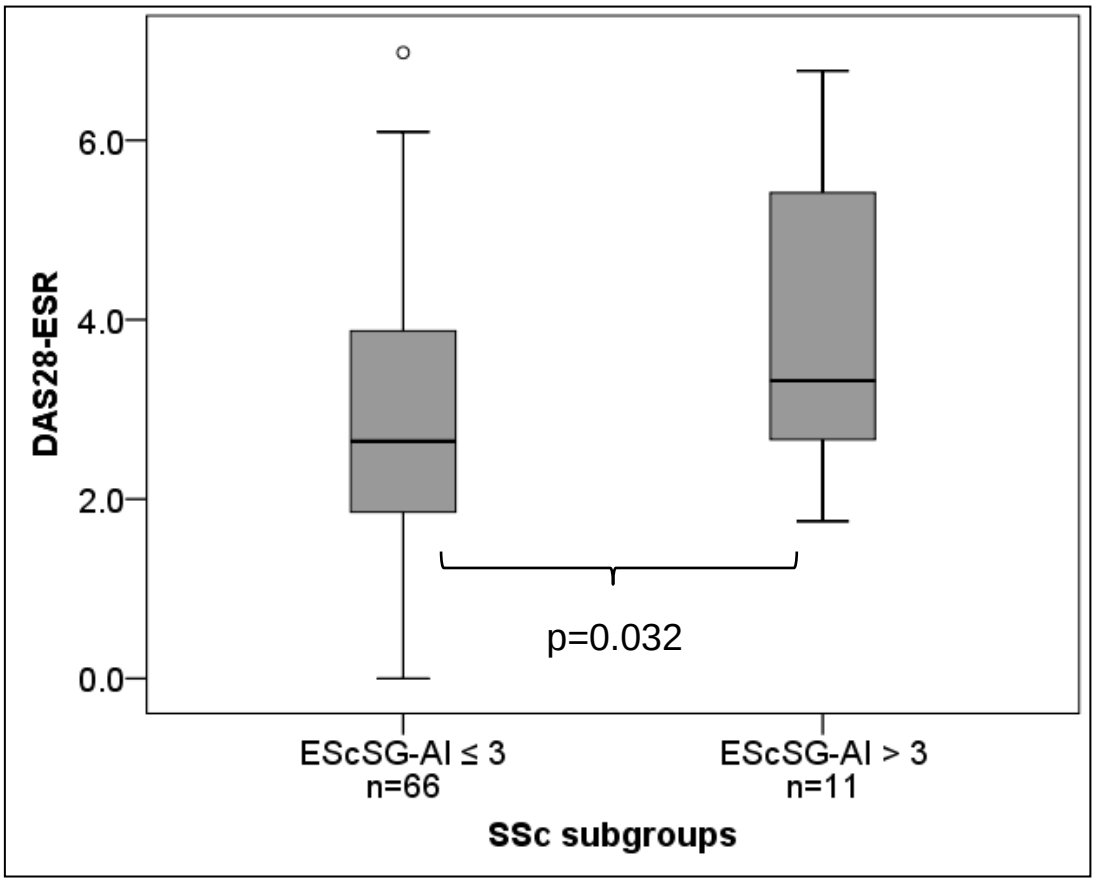
**Figure 7 Comparison of DAS28-ESR values of 77 patients with systemic sclerosis (SSc) to the control groups**




*RA: rheumatoid arthritis, RP: primary Raynaud's syndrome, HC: healthy control, DAS28-ESR: Disease Activity Score of 28 Joints using ESR. Statistical comparison was done by Mann-Whitney U test.*

Concerning disease activity, SSc patients with an EScSG-AI score higher than 3 (n=11) had significantly higher DAS28-ESR, SDAI and CDAI values than patients with an EScSG-AI score of 3 or less (n=66) ($p<0.05$) (Figure 8). No significant difference was found regarding DAS28-CRP in these particular subgroups (p=0.064).

**Figure 8 Comparison of DAS28-ESR values of systemic sclerosis (SSc) subgroups based on disease activity**




*EScSG-AI: European Scleroderma Study Group Activity Index, DAS28-ESR: Disease Activity Score of 28 Joints using ESR, p: significance of the Mann-Whitney U test comparing the two subgroups*

Significant difference was found in the values of DAS28-ESR between SSc patients with ESR ≤30 mm/h and >30 mm/h (p=0.014), and regarding SDAI and DAS28-CRP values between SSc patients with CRP≤5mg/l and >5mg/l (p=0.011, p=0.048 respectively).

Regarding functional disability, all four articular indices distinguished SSc patients with HAQ-DI<1 and patients with HAQ-DI ≥1 (p<0.001). Subgroups of RA based on HAQ-DI values (<1 vs. ≥1) showed similar results (p=0.05). No significant difference was found between the values of articular indices of SSc subgroups based on cutaneous subsets, disease duration (≤4 years and >4 years), MRSS (≤14 and >14) and HAI (≤2 and >2), presence or absence of digital ulcers, ulcers present on the extensor surface of the joints, and subcutaneous calcinosis (p>0.05).

### 5.3.5. Reliability and feasibility

ICC for the assessment of interobserver reliability of DAS28-ESR, DAS28-CRP, SDAI and CDAI was 0.89, 0.89, 0.71 and 0.70 respectively; Cronbach's alpha was 0.94, 0.92, 0.84 and 0.83 respectively ($p<0.001$). ICC evaluating intraobserver reliability of DAS28-ESR, DAS28-CRP, SDAI and CDAI was 0.98, 0.97, 0.92 and 0.92 respectively; Cronbach's alpha was 0.99, 0.98, 0.96 and 0.96 respectively ($p<0.001$). Each assessment lasted 3 to 5 minutes.

### 5.3.6. Comparison with the 8 joint counts

Similarly to the DAIs in question, the 8JTC and 8JSC showed significant correlation with measures of disease activity (EScSG-AI, MSAI and VAS-physician) and with measures of disability (HAQ-DI, CHFS, qDASH, VAS-overall) (Table 11). However, the 8JTC did not discriminate between patients with SSc and PR (Table 10). Moreover, 8JTC failed to discriminate SSc patients with an EScSG-AI score higher than 3 (n=11) and patients with an EScSG-AI score of 3 or less (n=66), while 8JSC did not discriminate between SSc patients with HAQ-DI<1 and those with HAQ-DI≥1 (data not shown). Neither 8JTC, nor 8JSC distinguished between subgroups of SSc patients with high and low inflammatory markers (CRP (≤5 vs. >5 mg/l) and ESR (≤30 vs. >30 mm/h)).

# 6. DISCUSSION

## 6.1. Investigation of distribution of joint involvement in SSc

To our knowledge this was the first study analysing the frequency of joint tenderness and swelling on clinical examination of different joints in a multicentre SSc patient cohort. The joint distribution described in our multicentre study was similar to the one seen in our single centre SSc cohort. Clinical joint involvement, as tenderness and swelling was most prominent in the hands in both cohorts, in accordance with previous results [30]. The higher prevalence of symptoms regarding most of the joints in the multicentre cohort compared to the single centre SSc cohort can be explained by the different inclusion criteria in the two studies. Only patients with at least two swollen and tender joint were enrolled in the multicentre cohort, while patients even without any articular symptoms were also included in the single centre study.

The dominance of symptoms in the second and third digits are in concordance with findings in RA [127]. As the right side is more often the dominant one, higher frequency of swelling and tenderness of the right hand joints might be due to more intense use. This is in concordance with our previous results, where more severe restriction of range of motion was found in the dominant hand of patients with SSc [124]. The reason for not being able to demonstrate this difference between the left and right side of patients in our single centre cohort, might be due to the smaller patients number in this study.

Clinical DIP joint involvement, such as tenderness (2-14%) and swelling (0-4%) were found to be far less frequent in both, single and multicentre SSc cohorts than radiographic involvement (7-54 %) of the same joints reported in previous studies [128]. This might be explained by two factors. (1) Joint tenderness and swelling are reversible abnormalities that can subside spontaneously or due to drugs (eg. low dose corticosteroids), while radiographic evidence of chronic inflammation, like erosions and joint space narrowing remain. (2) The much lower prevalence of clinically detectable inflammation in the DIP joints might suggest a non-inflammatory nature of joint involvement. Hand osteoarthritis is quite common, particularly in middle-aged women, so coexistence of SSc and osteoarthritis might at least partly explain frequent non-inflammatory DIP involvement described in patients with SSc.

In our single centre study physical examination of the patients with SSc did not demonstrate a higher prevalence of tenderness or swelling in the DIP joints compared to patients with RA. This prompts there is no need for supplementing the 28 joint counts with

the DIP-counts in SSc (Figure 1). However, radiologic investigations using X-ray, US or MRI showed a high prevalence of DIP involvement (20-72%) in previous reports [62, 128]. It must also be noted that in other diseases, such as psoriatic arthritis, the 68/66 joint counts were found to be more reliable, than the 28 joint counts [129].

Synovitis, muscle weakness and decreased DLCO are all known unfavourable prognostic factors in SSc [130-132]. This might explain the differences found between the "Arthritis group" and the "Non-arthritis group" in the DeSScipher Study.

All patients with SSc should be screened for synovitis by physical examination at least upon diagnosis of the disease and annual follow-up visits. Investigation of inflammatory joint involvement and increasing articular damage should receive particular attention in the follow-up of patients with articular complaints; decreased DLCO or muscle weakness.

### 6.2. Cross-cultural adaptation and validation of the Hungarian version of CHFS in SSc and RA

The cross-cultural adaptation and validation of the CHFS has been carried out according to international standards. The forward-backward translation of the test was done without any difficulties; the patients found the questions of the pre-final version clear and did not recommend any modifications. The majority of patients filled out the CHFS in less than three minutes. Feasibly of CHFS was proven, since its cost, equipment (pen, paper, printing), time (<3 minutes for filling in, <2 minutes for assessing results) and training (none) requirements are minimal.

According to the CHFS test results there was not any considerable difference between the hand function of the patients with RA and the patients with SSc, however there was a significant difference between the control groups and the patient groups. Many previous studies found significant difference between the hand function of patients with dcSSc and lcSSc measured by CHFS and other test [23, 25, 111], while Hesselstrand *et al* [133] did not find any difference. In our study no significant difference was found between the two cutaneous subgroups by the tests referring to hand damage. However, the DAS28-ESR, ESR, and CRP that refer to inflammation and disease activity were remarkably higher in the lcSSc group – that usually has better hand function – than the dcSSc group. (Table 8).

According to the number of maximal and minimal scores achieved in our study the Hungarian version of the CHFS is capable of measuring hand status of SSc and RA patients; no floor and ceiling effect was found.

In our study the CHFS was found to be two dimensional by principal component analysis. It was reported to be three dimensional by the original French study [134]; while we did not find any further data regarding this aspect of the test in other studies.

The high Cronbach's alpha value – similarly to that seen in the French study [134] – shows good internal consistency. Regarding reproducibility, the repeated measurements of CHFS showed high ICC, as well as in previous studies [8, 109, 134]. This means overall reliability of the test did not change during its cross-cultural adaptation to Hungarian.

In accordance with previous studies CHFS showed the strongest correlation with HAQ-DI in patients with SSc ($\rho$=0.709) and RA ($\rho$=0.831) [17, 43, 111, 112, 133]. This indicates that there is strong association between the functional state of the hands and the patients' general functional state and self-efficacy. The CHFS indicated the condition of the hands in both disease groups in agreement with the HAI, which demonstrates anatomic damage of the hands. There was only partial correspondence between CHFS and disease activity, because it showed positive correlation with the DAS28, but it did not show significant correlation with ESR, or with CRP. Testing of discriminant validity showed that the CHFS is capable of defining diverse levels of disability in patients with different degree of hand damage.

The limitations of this study were there relatively small number of patients and its cross-sectional nature. According to previous international publications [111, 135] the CHFS can be successfully used for follow-up of hand function in rheumatic patients; and the values of "sensibility to change" and „minimally important difference" of CHFS have been assessed. The Hungarian version of the CHFS has yet to be assessed regarding responsiveness.

The strength of our study was the contribution of various patient groups and good statistical results in the test validation procedure.

The CHFS provides a fast and simple way for assessment of hand related disability in both, clinical practice and clinical trials. It is a good alternative of the HAQ-DI, focusing on hand involvement instead of global disability.

### 6.3. Validation of articular DAIs in SSc

Our results indicate that DAS28-ESR, DAS28-CRP, SDAI and CDAI composite scores are valid measures for the assessment of arthritis in SSc. As observed in RA, the simplified indices (CDAI and SDAI) showed a very similar performance to the DAS28-ESR and the DAS28-CRP, and the four DAIs highly correlated with each other [122]. This means the simpler SDAI and CDAI have similar value in the assessment of SSc compared to DAS28-ESR and DAS28-CRP, with the additional advantage of not needing a computer – or even laboratory results in case of CDAI – for their calculation.

The strength of association between each DAI and the HAQ-DI (r=0.48-0.50) in the patients with SSc corresponded with previous data in RA [118]. While disability caused by hand contractures is more obvious, the strong correlation of joint inflammation (DAS28-ESR, DAS28-CRP, SDAI, CDAI) and overall disability (HAQ-DI) indicates that joint inflammation itself can also cause a significant amount of functional disability.

Articular tenderness was a frequent finding in SSc (Table 5 and Figure 1). All four investigated DAIs showed strong correlation with pain, and particularly strong with joint pain (Table 8). The other potential sources of pain, including skin ulcers did not influence the results. No significant difference was found in the values of articular indices of subgroups based on the presence or absence of skin ulcers and subcutaneous calcinosis (data not shown). This means damage did not influence the values of DAS28-ESR, DAS28-CRP, SDAI and CDAI in SSc. In this study no correlation was found between the scores of articular indices and the measures representing mainly structural damage, such as HAI, Delta-FTP and CoC28. Moreover, disease duration and age did not show any correlation with the articular DAIs either, which also support that these indices rather represent articular disease activity of SSc, than articular damage. This was also underlined by the results of the principal component analysis.

The strong concerns about non-articular hand involvement (i.e. subcutaneous calcinosis, digital ulcers) and joint contractures interfering with the assessment of joint inflammation by physical examination in patients with SSc seem to be resolved. Upon physical examination, patients with even very sever hand deformities did not necessary have any joint tenderness at all. Of note, seriously infected digital ulcers can result in high acute phase reactants and consequently falsely high DAS-ESR, DAS28-CRP and SDAI values. In these cases the DAI might be repeated after treatment of the infection. Tenderness of the surrounding skin of digital ulcers and subcutaneous calcinosis must also be taken into

account. However, this only means that the result of the DAIs should be interpreted keeping in mind the potential interfering factors noted during the physical examination of the patients.

Face validity of the DAIs in SSc was proved by (1) the presence of synovitis – characterized by joint tenderness and/or swelling, (2) the strong association found between elevated levels of acute phase reactants and the presence of synovitis and (3) presence of radiographic joint changes similar to that seen in RA [2, 29, 94]. Construct validity of the articular DAIs was established by significant correlations with measures of disease activity. When interpreting the strength of correlation between the articular DAIs and measures of global disease activity (EScSG-AI, MSAI), it should be kept in mind, that as opposed to RA, SSc is a multidimensional disease, where global disease activity can be represented by various features (skin, lung, heart, vascular and musculoskeletal involvement).

The DAIs also significantly correlated with measures of functional ability (HAQ-DI, qDASH, CHFS) and physical health related quality of life (SF36 PCS). QDASH and CHFS are measures of functional ability of upper extremities, while HAQ-DI has been shown to account for hand involvement in 75% [17]. The high correlation of the articular indices with these three measures can be explained by the fact, that the majority of the joints assessed in the 28 joint counts refer to the upper limb. A high proportion of the patients did not have any articular complaints, but floor and ceiling effects were not present at either of the articular DAIs.. We must note that cohort enrichment was performed to ensure the proper number of patients with early disease and dcSSc. Since synovitis is more frequent in patients with early disease and dcSSc, in an unselected clinical setting synovitis is probably less frequent than in our cohort. However, this does not decrease the value of the DAIs in SSc patients with inflammatory joint complaints.

All four indices were able to discriminate between SSc and RA patients, SSc and PR, SSc and healthy controls. DAS28-ESR, CDAI and SDAI scores were able to discriminate between SSc subgroups, and active vs. inactive disease based on EScSG-AI results, while DAS28-CRP failed this test. All four indices were able to discriminate between SSc patients with and without significant disability according to HAQ-DI.

Regarding reliability**,** the DAS28-ESR performed best among the four investigated indices, however good interobserver and intraobserver reliability was found regarding all four articular indices.

Feasibility was proven for all four articular DAIs. The joint examination and completion of the VAS-s lasted less than five minutes per patient. Additional training is not required for rheumatologists experienced in the assessment of RA patients.

The 8JTC and 8JSC seemed to be intriguing alternatives of the DAIs investigating 28 joints, as they require less time and effort. Unfortunately, even though the 8 joint counts showed similarly strong correlation with measures of disease activity and disability as the investigated four DAIs, their discriminative ability was poor. These simpler measures do not seem appropriate outcome measures for SSc.

In this study DAS28-ESR showed the best results regarding construct validity, discrimination and reliability. However, the better performance of DAS28-ESR compared to DAS28-CRP might be explained by the presence of ESR and absence of CRP in the item list of EScSG-AI. In the context of outpatient care, where prompt laboratory results are not available, CDAI can be used.

Our study has some limitations: (1) A relatively high number of patients did not have any tender or swollen joints. (2) Further study is needed to assess the articular DAIs regarding sensitivity to change, predictive value and cut-offs for the active, moderately active arthritis, and remission of arthritis in SSc.

Avouac *et al* [29] found strong association between synovitis, joint contractures, and tendon friction rubs in multivariate analysis, and reported that contractures develop during the first couple of years of the disease. This was confirmed by our previous and also our current findings, as the number of contractures did not differ in SSc patients with disease duration of four years or less compared to those with longer disease duration [124]. Strict follow-up of articular disease activity using the DAIs allows early pharmacologic treatment, which might prevent the development of joint contractures in patients with SSc [2]. However, so far there is no evidence based therapy for arthritis and prevention of joint contractures in SSc, only some reassuring observations are recently available [58, 128]. Therapeutic approach is mainly based on experience gained in RA. Randomized controlled clinical trials focusing on the treatment of joint involvement in SSc are highly warranted [128].

In summary, all investigated DAIs can be used in clinical trials and later on they might also be used in daily clinical practice for assessing articular disease activity in patients with SSc.

# 7. NEW RESULTS

7.1.1. In our study of clinical joint involvement in SSc we found, that distribution of joint swelling and tenderness by physical examination were similar to each other in patients with SSc. Joint swelling in SSc was rarer in the large joints (shoulders, elbows and knees), compared to the wrists and small joints of the hands in patients with SSc.

7.1.2. On comparison of our SSc and RA cohort, distribution of joint tenderness and joint swelling was similar in these two diseases. Tenderness was significantly more frequent in some small (PIP, MCP, wrist) and large (shoulder and knee) joints of the patients with RA compared to the patients with SSc. We found DIP tenderness and swelling was not more frequent in the SSc study group, than in the RA cohort, meaning the extension of 28 joint counts with the DIP joints for patients with SSc is probably not necessary.

7.1.3. The second and third fingers were the most often affected in the patients with SSc and also in the RA cohort. Joint tenderness and joint swelling seem to be slightly more frequent on the right side of patients with SSc. This suggests, that overuse of joints may result in worse clinical outcome.

7.1.4. Based on our multicentre SSc cohort, disease duration, cutaneous subset and antibody status do not seem to affect the distribution of joint tenderness and swelling in SSc.

7.1.5. The similar results of the single centre and the multicentre study prove feasibility of assessing joint synovitis by physical examination in SSc by rheumatologist without any additional training.

7.2.1. We were the first in Hungary who used the CHFS patient self-questionnaire. We have successfully completed its cross-cultural adaptation to Hungarian with the internationally standardized forward-backward translation technique. We have proven the validity of the Hungarian CHFS regarding truth, discrimination and feasibility.

7.2.2. We found no significant difference regarding hand function measured by CHFS in our consecutive patients with SSc and RA.

7.3.1. We were the first to validate and use the DAS28-ESR, DAS28-CRP, SDAI and CDAI tests in patients with SSc. We have found that these DAIs are able to assess arthritis in patients with SSc authentically, regarding both, truth and discrimination.

7.3.2. We have resolved the concerns about the many different aspects of hand involvement (digital ulcers, subcutaneous calcinosis, contractures) confounding the results of the DAIs. DAS28-ESR showed the best results in the validation procedure among the four investigated DAIs.

7.3.3. We found no significant difference in articular disease activity of SSc patients with early (disease duration 4 years or less) and late disease (disease duration more than 4 years).

## 8. CONCLUSIONS

Articular involvement is one of the most important factors of disability leading to decreased health related quality of life in SSc. Joint contractures develop early, in the very first 4 years of the disease on the ground of synovitis and fibrotic processes. Both, inflammatory joint involvement and joint contractures affect primarily the hands and wrists of the patients with SSc. Patients' dominant hand is usually in worse state than, their non-dominant hand. This prompts that; overuse of the hand joints enhances joint inflammation and damage.

Presence of digital ulcer, subcutaneous calcinosis or joint contractures might complicate the assessment of joint tenderness and swelling in some patients with SSc. However, physical examination of the joints should be carried out at least at establishment of the diagnosis of SSc and at annual follow-up visits. Special attention is needed in SSc patients with articular complaints, decreased DLCO or muscle weakness.

Cross-cultural adaptation and validation of commonly used patients' self-questionnaires, such as the CHFS allows international collaboration in SSc studies. This is particularly important due to the low prevalence of the disease.

Similarly to RA, prevention of development of joint contractures might be possible with early aggressive treatment of synovitis in SSc. So far treatment of synovitis is largely based on the experience gained in RA, because there are very few studies addressing treatment of arthritis in SSc. Validation of the articular DAIs allows their use as outcome measures in SSc drug trials. However, their sensitivity to change and cut points of remission, low and high disease activity regarding these DAIs need to be yet established.

Fast, simple and valid tools help proper follow-up of patients in clinical practice. These articular DAIs might allow a "treat to target attitude" [4] in the management of SSc patients with synovitis in the future.

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## 10. ADDENDUM

### The Hungarian version of the Cochin Hand Function Scale

**DHI Duruöz Hand Index**

**Kérjük jelölje X-szel a jelen állapotára jellemző megfelelő választ!**

| Képes-e | **nehézség nélkül** | **kis nehézséggel** | **közepes nehézséggel** | **nagy nehézséggel** | **szinte lehetetlen megcsinálni** | **lehetetlen megcsinálni** |
|---|---|---|---|---|---|---|
| 1. megtartani egy tálat? | | | | | | |
| 2. megfogni és felemelni egy tele üveget? | | | | | | |
| 3. megtartani egy tányért tele étellel? | | | | | | |
| 4. folyadékot önteni üvegből pohárba? | | | | | | |
| 5. lecsavarni egy előzőleg már kinyitott konzervüveg tetejét? | | | | | | |
| 6. húst vágni késsel? | | | | | | |
| 7. felszúrni dolgokat villával? | | | | | | |
| 8. gyümölcsöt hámozni? | | | | | | |
| 9. begombolni az ingét? | | | | | | |

| Képes-e | **nehézség nélkül** | **kis nehézséggel** | **közepes nehézséggel** | **nagy nehézséggel** | **szinte lehetetlen megcsinálni** | **lehetetlen megcsinálni** |
|---|---|---|---|---|---|---|
| 10. fel- és lehúzni a cipzárt | | | | | | |
| 11.megnyomni egy új tubus fogkrémet? | | | | | | |
| 12. hatékonyan használni a fogkefét? | | | | | | |
| 13. leírni tollal egy rövid mondatot? | | | | | | |
| 14. megírni tollal egy levelet? | | | | | | |
| 15. elfordítani az ajtógombot? | | | | | | |
| 16. ollóval papírt vágni? | | | | | | |
| 17. felvenni érméket az asztalról? | | | | | | |
| 18. elfordítani a kulcsot a zárban? | | | | | | |

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# 14. LIST OF PUBLICATIONS RELATED TO THE SUBJECTS INCLUDED IN THE THESIS

## 14.1. Papers

1. Jaeger VK, Distler O, Maurer B, Czirják L, Lóránd V, Valentini G, Vettori S, Del Galdo F, Abignano G, Denton C, Nihtyanova S, Allanore Y, Avouac J, Riemekasten G, Siegert E, Huscher D, Matucci-Cerinic M, Guiducci S, Frerix M, Tarner IH, Garay Toth B, Fankhauser B, Umbricht J, Zakharova A, Mihai C, Cozzi F, Yavuz S, Hunzelmann N, Rednic S, Vacca A, Schmeiser T, Riccieri V, Garcia De La Peña P, Gabrielli A, Krummel-Lorenz B, Martinovic D, Ancuta C, Smith V, Müller-Ladner U, Walker UA. Functional disability and its predictors in systemic sclerosis: a study from the DeSScipher project within the EUSTAR group. Rheumatology (Oxford) 2018;57:441-450. **IF:4.818 (2016)**

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### 14.2. Published Abstracts

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2. Lóránd V, Kisné Bálint Z, Komjáti D, Németh B, Minier T, Kumánovics G, Farkas N, Jakabné Hamar A, Czirják L, Varjú C. Disease activity, hand function and quality of life in systemic sclerosis and rheumatoid arthritis. Wien Klin Wochenschr, 2014:Suppl.126:S220-S221.

3. Lóránd V, Kisné Bálint Z, Komjáti D, Németh B, Farkas N, Jakabné Hamar A, Minier T, Kumánovics G, Sarlós DP, Czirják L, Varjú C. A kézízületi károsodás, kézfunkció és életminőség vizsgálata szisztémás sclerosisban és rheumatoid arthritisben Magyar Reumatológia 2014;55:151.

# 15. LIST OF PUBLICATIONS NOT RELATED TO THE SUBJECTS INCLUDED IN THE THESIS

## 15.1. Papers

1. Kecse-Nagy C, Szittner Z, Papp K, Hegyi Z, Rovero P, Migliorini P, Lóránd V, Homolya L, Prechl J. Characterization of NF-κB Reporter U937 Cells and Their Application for the Detection of Inflammatory Immune-Complexes. PLoS One. 2016;27:e0156328 **IF:2.806**

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**15.2. Published Abstracts**

1. Jaeger VK, Czirjak L, Lóránd V, Valentini G, Vettori S, Del Galdo F, Abignano G, Distler O, Maurer B, Denton C, Nihtyanova S, Allanore Y, Avouac J, Riemekasten G, Siegert E, Huscher D, Matucci-Cerinic M, Guiducci S, Frerix M, Tarner IH, Garay-Toth B, Ananieva LP, Cozzi F, Yavuz S, Hunzelmann N, Vacca A, Schmeiser T, Rednic S, Riccieri V, Krummel-Lorenz B, Gabrielli A, Garcia De La Peña P, Ancuta C, Müller-Ladner U, Walker UA. Functional Disability and Its Predictors in Systemic Sclerosis: A Study from the Desscipher Project within the European Scleroderma Trials and Research Group. Arthritis Rheum. 2016;68:2386-2387.

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# Validation of disease activity indices using the 28 joint counts in systemic sclerosis

**Veronika Lóránd[1], Zsófia Bálint[1], Dalma Komjáti[1], Balázs Németh[1], Tünde Minier[1], Gábor Kumánovics[1], Nelli Farkas[2], László Czirják[1] and Cecília Varjú[1]; on behalf of the DeSScipher Consortium and contributing EUSTAR centers***

## Abstract

**Objectives.** To validate the Disease Activity Score 28 using ESR (DAS28-ESR) and CRP (DAS28-CRP), the Simplified Disease Activity Index and the Clinical Disease Activity Index used in RA for SSc patients.

**Methods.** Seventy-seven SSc patients, 40 RA patients, 20 patients with primary RP (PRP) and 28 healthy volunteers were assessed. Besides the disease activity composite indices, the European Scleroderma Study Group Activity Index (EScSG-AI), the HAQ-DI, the Cochin Hand Function Scale and the Short Form Health Survey (SF36) were evaluated. The validation procedure included the assessment for truth, discrimination and feasibility.

**Results.** DAS28-ESR, DAS28-CRP, Simplified Disease Activity Index and Clinical Disease Activity Index showed significant correlation with EScSG-AI, HAQ-DI, Cochin Hand Function Scale and the physical component of SF36 ($P < 0.001$). All four indices discriminated patients with SSc from RA, PRS and healthy controls, respectively ($P < 0.01$). With the exception of DAS28-CRP, the other three indices also discriminated between subgroups of SSc based on value of EScSG-AI ($\leqslant 3$ and $>3$) ($P < 0.05$). All four disease activity composite indices showed a good inter- and intraobserver reliability based on repeated measures of two independent investigators ($P < 0.001$).

**Conclusion.** All four disease activity composite indices were found to be valid measures for assessing arthritis in SSc. DAS28-ESR showed the best performance regarding reliability and construct validity.

**Key words:** systemic sclerosis, scleroderma, arthritis, disease activity, validation, DAS28.

**Rheumatology key message**

- Assessment of 28 joint count based disease activity scores are appropriate instruments in SSc.

## Background

RA is a chronic inflammatory disease characterized by polyarthritis leading to destructive joint disease which can be reduced or prevented by controlling the disease activity. Several disease activity composite indices (DAIs)—combining the number of tender and swollen joints with laboratory markers of inflammation, and the opinion of patient/physician—have been developed and validated including Disease Activity Score 28 using ESR (DAS28-ESR), DAS28 using CRP (DAS28-CRP), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) [1–6]. All four indices show high accordance with joint damage progression and functional condition of the patients, whereas the most stringent remission criteria are defined by SDAI and CDAI [7]. These particular composite indices contributed to the development of the treat to target approach for the management of RA [8].

[1]Department of Rheumatology and Immunology, Medical Center and [2]Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary

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Correspondence to: László Czirják, Department of Rheumatology and Immunology, Medical Center, University of Pécs, Pécs, Akác utca 1, H-7632, Hungary. E-mail: czirjak.laszlo@pte.hu

SSc is a systemic connective tissue disease characterized by vasculopathy, tissue fibrosis and autoimmune phenomena. Besides the skin and multiple internal organ manifestations including heart, lung, gastrointestinal and renal involvement, there is a significant musculoskeletal involvement resulting in disability and reduction of quality of life. The articular involvement, including arthralgia, swelling and joint contractures is usually most prominent on the hands [9]. The physical assessment of hand joints in SSc can be confounded by swelling and tenderness of the skin. Moreover digital ulcers, subcutaneous calcinosis and joint contractures may also cause difficulty during palpation of the joints [10, 11].

The prevalence of arthritis detected by physical examination in unselected SSc patients varies between 7 and 60%, among the different reports. The wide range might be due to lack of a standardized method of assessment, lack of consensus on the definition of synovitis in SSc, moreover, the cohorts investigated in these particular studies widely differ in terms of disease duration and the proportion of lcSSc and dcSSc cases [12–20].

The largest SSc cohort assessed for articular involvement was the EUSTAR database (n = 7286). Avouac *et al.* [14] found a prevalence of synovitis, defined by tender and swollen joints, in 16% of the patients and a significantly higher prevalence in dcSSc (20%, n = 2393), than in lcSSc (13.5%; n = 4210).

The 0–8 joint count (assessing swelling and tenderness in the MCP-rows, wrists, elbows and knees) has been used in at least four randomized controlled clinical trials, however, they did not detect significant change over 12–24 months, except for the Scleroderma Lung Study. In the Scleroderma Lung Study a significant decline was detected in the joint swelling count over 1 year follow-up [11, 21–24]. In a small SSc pilot study (n = 7), investigating intravenous immunoglobulins, significant improvement of joints was detected over 6 months using the Ritchie-index, an articular index assessing tenderness in 52 joints on a 4 point Likert scale [25, 26]. DAS28-ESR has been successfully used as an outcome measure for 27 patients with SSc in an observational study assessing the efficacy of abatacept and tocilizumab during 11 month [27].

According to Clements *et al.* [11] joint assessment by physical examination in SSc has face and construct validity, but other aspects of validity need to be examined. At presents there is no fully validated outcome measure for assessing synovitis in SSc [11]. The aim of our study was to validate the RA-related DAIs in SSc. The validation procedure included the assessment for truth, discrimination and feasibility.

## Patients and methods

### Patients

Seventy-seven patients with SSc [mean (S.D.) age: 56.3 (11.8) years] fulfilling the 2013 ACR/EULAR classification criteria where included from the Rheumatology and Immunology Department, Medical Center of the University of Pécs, which is a tertiary care unit [28]. The patients were classified into lcSSc and dcSSc subgroups according to the criteria of LeRoy and Medsger [29].

The following exclusion criteria were defined: end stage internal organ involvement (dialysis required, continuous oxygen therapy, estimated left ventricular ejection fraction <30% on echocardiography); significant joint pain or disability caused by other disorders (e.g. gout, OA, recent bone fracture etc.); and inability to cooperate.

Cohort enrichment was performed in order to increase the proportion of patients with early disease defined in this particular case as disease duration <4 years) and dcSSc. All consecutive patients with early disease fulfilling the criteria above were enrolled into the study during the recruitment period, while enrolment of consecutive patients with long standing disease was stopped after reaching a predefined number of patients (n = 55).

Forty consecutive patients with RA [mean (S.D.) age: 59.3 (8.1) years] fulfilling the 2010 ACR/EULAR classification criteria [30], 20 patients with primary RP (PRP) [mean (S.D.) age: 41 (13.3) years] and 28 healthy volunteers [mean (S.D.) age: 51.0 (15.6) years] were included as control groups. The control groups were matched in gender ratio to the SSc study group.

The subjects' written informed consent was obtained according to the Declaration of Helsinki (updated 2008). The study was approved by the Regional and Institutional Research Ethics Committee, Clinical Center, University of Pécs (4906/2013) and the Hungarian National Ethics Committee (IF-6720-6/2015.).

## Assessments

The articular DAIs were calculated according to the original formulas [3–6]. The DAS28-ESR is computed from the 28 joint swelling count (28JSC), the 28 joint tenderness count (28JTC), patient's assessment of global health on a 100 mm visual analogue scale (VAS-GH) and the ESR [3]. DAS28-CRP is calculated with slight modification of the DAS28-ESR formula, using the same variables, except for using CRP level (in mg/dl) instead of ESR [5].

$$\text{DAS28-ESR} = 0.56*\sqrt{28\text{JTC}} + 0.28*\sqrt{28\text{JSC}} + 0.70*\ln(\text{ESR}) + 0.014*\text{VAS} - \text{GH}\,(\text{range}: 0.49 - 9.08)$$

$$\text{DAS28-CRP} = 0.56*\sqrt{28\text{JTC}} + 0.28*\sqrt{28\text{JSC}} + 0.36*\ln(\text{CRP} + 1) + 0.014*\text{VAS} - \text{GH} + 0.96\,(\text{range}: 1.21 - 8.48)$$

$$\text{SDAI} = 28\text{JTC} + 28\text{JSC} + \text{CRP} + \text{VAS-Patient} + \text{VAS-Physician}\ (\text{range}: 0.1 - 86.0)$$

$$\text{CDAI} = 28\text{JTC} + 28\text{JSC} + \text{VAS-Patient} + \text{VAS-Physician}\,(\text{range}: 0 - 76)$$

SDAI is the numerical summation of the following variables: 28JTC, 28JSC, CRP (in mg/dl), patient's and physician's assessment of disease activity (in cm) on a 10 cm

VAS (VAS-Patient and VAS-Physician) [4]. CDAI is the numerical summation of the same variables as SDAI, except for CRP [6]. Besides the 28 joint count assessments, the number of tender and swollen DIPs was also assessed in each group. The eight joint counts concerning tenderness and swelling (8JTC and 8JSC, respectively) were calculated separately as described above.

Disease activity of SSc was assessed by the European Scleroderma Study Group Activity Index (EScSG-AI) and the Modified Scleroderma Activity Index (MSAI). EScSG-AI composes of five domains (skin, vascular, lung-heart, joint, laboratory), which are weighted and added up into a total score of 0–10 [31]. MSAI was derived from the EScSG-AI with different weighting of the items and incorporating additional measures, that is, patient's reported skin score, Health Assessment Questionnaire (HAQ) and the value of ratio of forced vital capacity and diffusing capacity for carbon monoxide (FVC/DLCO) [32].

Structural hand damage was examined by the Hand Anatomic Index (HAI) and the Delta Finger to Palm Distance (deltaFTP). HAI is defined as the maximum hand spread minus the closed hand span divided by maximum lateral hand height [33]. DeltaFTP is calculated by extracting the finger to palm distance, measured on the third finger during full finger flexion, from the distance measured between the same two points during maximal finger extension [34]. The number of joint contractures was assessed in the joints of the 28 joint count (CC28). Contracture was defined as present in a joint in case of at least 25% decrease in range of motion in at least one joint-movement direction [9].

All participants filled out a set of fully validated questionnaires on hand function, global function and quality of life [11, 35]. HAQ assesses the functionality of patients using 20 multiple-choice questions regarding activities of daily living [36]. Cochin Hand Function Scale (CHFS) is similar to HAQ; however it only refers to the hands [37]. The Quick Questionnaire of the Disability of the Hands, Arms and Shoulders (qDASH) measures disability of the upper extremities; it was validated to SSc by our research group [35]. The Scleroderma Health Assessment Questionnaire (SHAQ), in addition to the HAQ, contains also five VASs measuring the effect of lung and gastrointestinal involvement, digital ulcers, Raynaud's phenomenon and overall disease on the patient's life [38]. The Short Form Health Survey (SF36) assesses health related quality of life on two scales: the Mental Component Summary (MCS) and the Physical Component Summary (PCS) [39].

## Validation

The OMERACT filter was used to assess the validity of the DAIs including feasibility, truth and discrimination [40]. Construct validity was assessed by calculating the correlation between the particular articular indices and other instruments reflecting disease activity, joint involvement and hand function. Content validity was assessed by principal component analysis of outcome measures of disease activity and damage, and by looking for floor and ceiling effects. Floor and ceiling effects were considered present if $>15\%$ of respondents achieve the highest or lowest possible score. The minimum and maximum value of DAS28-ESR, DAS28-CRP and SDAI depend on the lowest and highest possible value of ESR and CRP, which were considered to be 2 and 100 mm/h in case of ESR, whereas $\leqslant 0.1$ and 10 mg/dl in case of CRP according to the literature [41]. Structural validity was assessed by testing unidimensionality of the DAIs with principal component analysis.

For testing interobserver reliability, two raters, an experienced rheumatologist (G.K.) and a young physician (V.L.) examined a subgroup of SSc patients ($n=20$) independently from each other. For testing intraobserver reliability, a subgroup of patients ($n=12$) was assessed by the same observer twice within 5 days assuming disease activity did not change within this period of time. The articular disease activity of the patients was considered stable during this interval. Discrimination was examined between the SSc and the control groups, then on SSc subgroups based on various characteristics: cutaneous subset, disease duration ($\leqslant 4$ and $>4$ years), Modified Rodnan Skin Score (MRSS) ($\leqslant 14$ and $>14$), EScSG-AI ($\leqslant 3$ and $>3$) [31], HAQ ($<1$ and $\geqslant 1$) [42], CRP ($\leqslant 5$ mg/l and $>5$), ESR ($\leqslant 30$ and $>30$ mm/h), HAI (($\leqslant 2$ and $>2$) [33, 35].

### Statistical analysis

Spearman correlation test was used to determine construct validity. Intra- and interobserver reliability was assessed by intraclass correlation coefficient (ICC) and Cronbach $\alpha$. Data regarding continuous variables are shown as mean (S.D.) or median, upper or lower quartiles, depending on normal distribution. Discrimination between subgroups was tested by Mann–Whitney test for continuous variables and with Chi-square test for categorical variables. Principal component analysis was used to test content and structural validity. SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses.

## Results

The main clinical manifestations of the SSc cohort are represented in Table 1. Clinical data and results of outcome measures regarding the four study groups are depicted in Table 2. The prevalence of tenderness and swelling of each joint in the SSc and the RA cohort is depicted in Figure 1. In the SSc group, the wrists, MCPs and PIPs were affected most often, while knee, elbow and DIP involvement was much less frequent. There was no significant difference in the number of tender DIPs and the number of swollen DIPs between RA and SSc patients. No significant difference was found in the composite indices in SSc patients with a disease duration $\leqslant 4$ years *vs* $>4$ years.

### Construct validity

DAS28-ESR, DAS28-CRP and SDAI showed a significant correlation with disease activity measured by the EScSG-

**Table 1** Clinical manifestations of the 77 patients with systemic sclerosis

| Clinical manifestations | SSc |
|---|---|
| Dc subset | 50 (65) |
| Lc subset | 27 (35) |
| ACA, n (%) | 21 (27) |
| Anti-topo I antibody, n (%) | 32 (42) |
| MRSS, median (IQR) | 15 (9–22) |
| Lung fibrosis on HRCT, n (%) | 55 (71) |
| FVC% <70%, n (%) | 8 (10) |
| DLCO% <70% n (%) | 47 (61) |
| PAH by right heart catheterization, n (%)[a] | 3 (4) |
| Diastolic dysfunction (n = 72), n (%)[b] | 36 (47) |
| Scleroderma renal crisis, n (%) | 1 (1) |
| Digital ulcer, n (%) | 15 (19) |
| Subcutaneous calcinosis on the hands, n (%) | 8 (10) |
| Contractures (in the joints of the 28 joint count), n (%)[c] | 43 (56) |
| Tendon friction rubs, n (%) | 19 (25) |
| EScSG-AI, median (IQR) | 1.5 (0.5–2.0) |
| MSAI, median (IQR) | 1.5 (1.0–2.5) |
| RA overlap, n (%)[d] | 3 (4) |
| Myositis, n (%) | 3 (4) |
| Number of tender joints out of 28, n (%) | |
| 0 | 40 (52) |
| 1–5 | 15 (19) |
| 6 or more | 22 (29) |
| Number of swollen joints out of 28, n (%) | |
| 0 | 52 (68) |
| 1–5 | 21 (27) |
| 6 or more | 4 (5) |

[a]PAH defined as right heart pressure >40 mmHg by right heart catheterization. [b]Diastolic dysfunction by transthoracic echocardiography. [c]Defined as present in a joint in case of at least 25% decrease in range of motion in at least one joint-movement direction, examined in the joints of the 28 joint count. [d]RA according to the 2010 ACR/EULAR classification criteria. FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; PAH: pulmonary artery hypertension, EScSG-AI: European Scleroderma Study Group Activity Index; MSAI: Modified Scleroderma Disease Activity Index.

AI and the MSAI (Table 3). A high correlation was observed between the articular disease activity assessed by the physician on VAS and DAS28-ESR as well as DAS28-CRP (Table 3).

The articular activity indices showed a strong correlation with measures of disability (HAQ, CHFS, qDASH, VAS-overall) (Table 3). SF36-PCS showed a significant correlation with all four articular DAIs, while SF36-MCS showed only weak correlation with SDAI and CDAI, and no correlation with DAS28-ESR and DAS28-CRP (Table 3). There was no correlation between the articular indices and the following parameters: age, disease duration, MRSS, HAI, deltaFTP, CC28 (data not shown).

### Content validity

Out of the 77 SSc patients 3.9, 10.4, 2.6 and 6.5% got the lowest possible score regarding DAS28-ESR, DAS28-CRP, SDAI and CDAI, respectively, while none of the patients reached the highest value regarding any of the four measures. When loading measures of or corresponding to disease activity (CRP, ESR, MSAI, EScSG-AI, MRSS, HAQ, VAS-fatigue), measures of joint involvement (CHFS, qDASH, joint pain), measures of quality of life (SF36-PCS, SF36-MCS), measures of structural joint damage (HAI, deltaFTP, CC28) and the investigated DAIs into a principal component analysis, 55% of the original information was summarized into the first two components. All four DAIs as well as MSAI, HAQ, VAS-fatigue, CHFS, qDASH, joint pain and SF36-PCS fell into the first component; whereas measures of structural damage (HAI, deltaFTP, CC28) fell into the second component.

### Structural validity

Principal component analysis was performed to check for the unidimensionality of the articular DAIs. The components were analysed as they are weighted in each index. All four indices were unidimensional; their components were grouped into a single factor, which explained 55.9, 56.8, 61.3 and 71.8% of the variance, for DAS28-ESR, DAS28-CRP, SDAI and CDAI, respectively.

### Discriminant validity

Significant differences were seen in these particular composite indices comparing patients with SSc and patients with RA, PRP and healthy controls (Fig. 2). Concerning disease activity, SSc patients with an EScSG-AI score higher than 3 (n = 11) had significantly higher DAS28-ESR, SDAI and CDAI values than patients with an EScSG-AI score of 3 or less (n = 66) ($P < 0.05$). No significant difference was found regarding DAS28-CRP in these particular subgroups ($P = 0.064$) (Fig. 3). Significant difference was found in the values of DAS28 between SSc patients with ESR ⩽30 mm/h and >30 mm/h ($P = 0.014$), and regarding SDAI and DAS28-CRP values between SSc patients with CRP ⩽5 mg/l and >5 mg/l ($P = 0.011$, $P = 0.048$, respectively).

Regarding functional ability, all four articular indices could differentiate between SSc patients with HAQ <1 compared with those with HAQ ⩾1 ($P < 0.001$). Subgroups of RA based on HAQ values (<1 and ⩾1) showed similar results ($P = 0.05$). No significant difference was found between the values of articular indices of SSc subgroups based on cutaneous subsets, disease duration (⩽4 years and >4 years), MRSS (⩽14 and >14) and HAI (⩽2 and >2), presence or absence of digital ulcers, ulcers present on the extensor surface of the joints, and subcutaneous calcinosis ($P > 0.05$).

### Reliability and feasibility

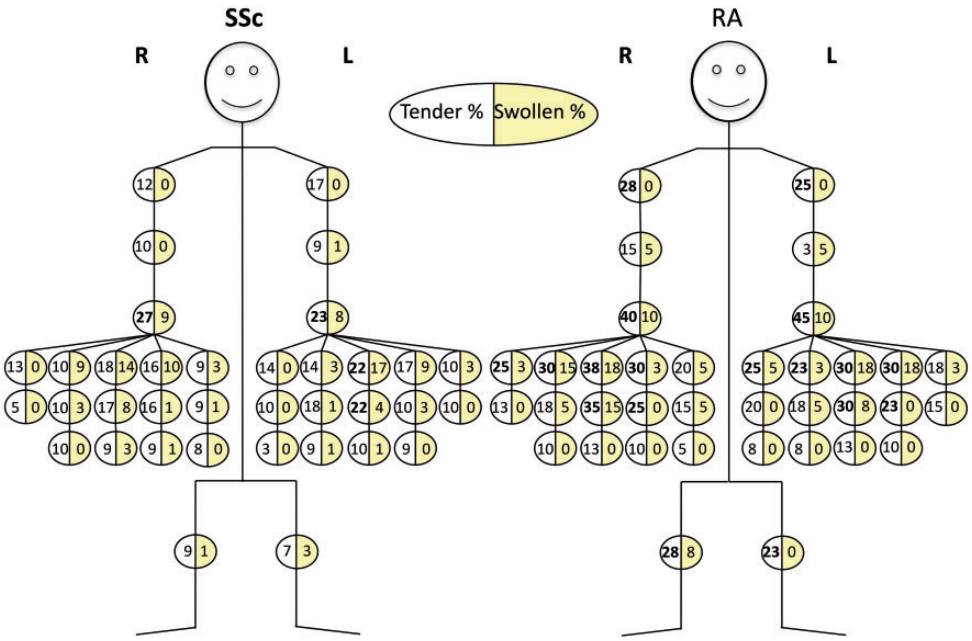
ICC for the assessment of interobserver reliability of DAS28-ESR, DAS28-CRP, SDAI and CDAI was 0.89, 0.89, 0.71, 0.70, Cronbach $\alpha$ was 0.94, 0.92, 0.84, 0.83, respectively ($P < 0.001$). ICC evaluating intraobserver

**Table 2** Clinical data of patients with SSc, RA, PRP and healthy volunteers

| Clinical data | SSc n = 77 | RA n = 40 | PRP n = 20 | HC n = 28 | RA *vs* SSc, P-value[a] | PRP *vs* SSc, P- values | HC *vs* SSc, P- values |
|---|---|---|---|---|---|---|---|
| Gender F/M, n (%) | 67/10 (87/13) | 36/4 (90/10) | 18/2 (90/10) | 25/3 (89/11) | 0.637 | 0.718 | 0.755 |
| Age, mean (S.D.) | 56.3 (11.8) | 59.3 (8.1) | 38.7 (13.5) | 51 (15.6) | 0.106 | 0.000 | 0.012 |
| Disease duration, mean (S.D.)[b] | 10.5 (9.5) | 15.2 (9.1) | 10.5 (9.6) | NA | 0.013 | 0.999 | NA |
| RF, n (%) | 18 (33)[c] | 26 (65) | 2 (10) | ND | 0.002 | 0.045 | NA |
| Anti-CCP, n (%) | 1 (2)[d] | 24 (60) | (0)[e] | ND | 0.000 | 0.569 | NA |
| DAS28-ESR, median (IQR) | 2.7 (1.98–3.93) | 3.59 (2.81–4.68) | 1.64 (1.3–2.04) | 1.65 (1.36–1.97) | 0.002 | 0.001 | <0.001 |
| DAS28-CRP, median (IQR) | 2.12 (1.49–3.41) | 3.42 (2.42–4.00) | 1.6 (1.27–1.88) | 1.33 (1.13–1.79) | 0.001 | 0.012 | <0.001 |
| SDAI, median (IQR) | 4 (1–15) | 12 (4–22) | 1 (0–5) | 0 (0–1) | 0.005 | 0.008 | <0.001 |
| CDAI, median (IQR) | 4 (1–15) | 11 (4–22) | 1 (0–5) | 0 (0–1) | 0.005 | 0.013 | <0.001 |
| CRP, median (IQR), mg/l | 2.2 (1.3–4.0) | 3 (1.7–5.0) | 0.5 (0.3–1.1) | 0.8 (0.5–2.3) | 0.326 | <0.001 | 0.011 |
| ESR, median (IQR), mm/h | 15 (8–26) | 18 (9–24) | 6 (4–10) | 8 (6–14) | 0.852 | <0.001 | 0.001 |
| HAQ, median (IQR) | 0.88 (0.13–1.38) | 1.31 (0.91–1.75) | 0 (0–0.78) | 0 (0–0) | 0.007 | 0.001 | <0.001 |
| QDASH, median (IQR) | 32 (14–48) | 42 (26–59) | 8 (5–23) | 0 (0–6) | 0.023 | 0.003 | <0.001 |
| CHFS, median (IQR) | 7 (2–19) | 12 (3–24) | 1 (0–6) | 0 (0–0) | 0.396 | 0.002 | <0.001 |
| HAI, median (IQR) | 2.81 (2.19–3.4) | 3.01 (2.57–3.71) | 3.85 (3.35–4.6) | 4.05 (3.49–4.43) | 0.16 | <0.001 | <0.001 |
| FTP, median (IQR) | 19 (11–27) | 14 (8–21) | 0 (0–6) | 0 (0–7) | 0.041 | <0.001 | <0.001 |
| deltaFTP, median (IQR) | 76 (65–87) | 76 (68–86) | 92 (87–96) | 94 (89–100) | 0.97 | <0.001 | <0.001 |
| SF36 PCS, median (IQR) | 37 (29–46) | 34 (27–39) | 50 (37–57) | 56 (50–58) | 0.071 | 0.001 | <0.001 |
| SF36 MCS, median (IQR) | 49 (37–59) | 46 (29–59) | 38 (26–54) | 57 (52–59) | 0.258 | 0.014 | 0.105 |
| 8JTC, median (IQR) | 0 (0–3) | 2 (0–5) | 0 (0–1) | 0 (0–0) | 0.005 | 0.135 | 0.001 |
| 8JSC, median (IQR) | 0 (0–1) | 1 (0–2) | 0 (0–0) | 0 (0–0) | 0.040 | 0.004 | 0.001 |

[a]Value of significance in Mann–Whitney test or Chi-square test comparing the SSc cohort with each of the three control groups. [b]Time in years since first non-RP symptom for SSc patients. [c]n = 54 as data regarding these parameters were not available for all 77 SSc patients. [d]n = 50 as data regarding these parameters were not available for all 77 SSc patients. [e]n = 16 as data regarding these parameters were not available for all 20 PRP patients. HC: healthy control; F/M: female/male; ND: not done; NA: not applicable; DAS28-ESR: DAS28 using ESR; DAS28-CRP: DAS28 using CRP; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; QDASH: Quick Questionnaire of the Disability of the Hands, Arms and Shoulders; CHFS: Cochin Hand Function Scale; HAI: Hand Anatomic Index; FTP: Finger To Palm Distance; SF36 PCS: Short Form Health Survey Physical Component Scale; SF36 MCS: Short Form Health Survey Mental Component Scale; 8JTC: 8 joint tenderness count; 8JSC: 8 joint swelling count; PRP: primary Raynaud's syndrome.

**Fig. 1** Rate of SSc (n = 77) and RA (n = 40) patients with tenderness and swelling in examined joints



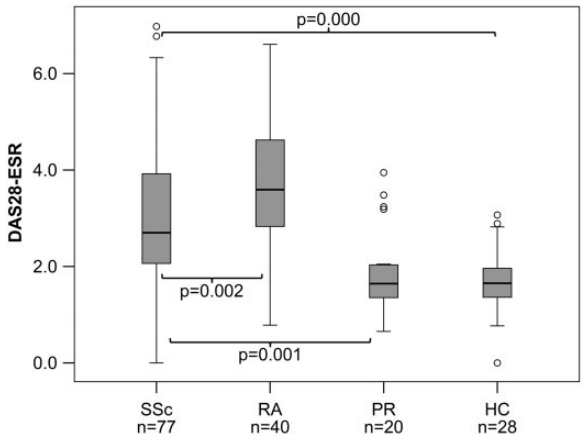

R: right, L: left. All values account for prevalence in percentages in the examined cohort. Percentages above 20 are written in bold.

**Table 3** Correlations of disease activity indices with functional status and disease activity measures in scleroderma (n = 77)

| SSc n = 77 | DAS28-ESR | DAS28-CRP | SDAI | CDAI | 8JTC | 8JSC |
|---|---|---|---|---|---|---|
| DAS28-ESR | – | 0.930[a] | 0.889[a] | 0.878[a] | 0.845[b] | 0.686[b] |
| DAS28-CRP | 0.930[a] | – | 0.952[a] | 0.934[a] | 0.850[b] | 0.718[b] |
| SDAI | 0.889[a] | 0.952[a] | – | 0.995[a] | 0.812[b] | 0.716[b] |
| CDAI | 0.878[a] | 0.934[a] | 0.995[a] | – | 0.814[b] | 0.717[b] |
| MSAI | 0.402[a] | 0.356[b] | 0.366[b] | 0.363[b] | 0.225[c] | 0.314[b] |
| EScSG-AI | 0.344[b] | 0.337[b] | 0.355[b] | 0.345[b] | 0.255[c] | 0.317[b] |
| CRP | 0.299[b] | – | – | 0.201 | 0.079 | 0.117 |
| ESR | – | 0.253[c] | 0.181 | 0.151 | 0.093 | 0.137 |
| VAS-physician | 0.701[a] | 0.749[a] | – | – | 0.738[b] | 0.673[b] |
| HAQ | 0.495[a] | 0.485[a] | 0.477[a] | 0.486[a] | 0.344[b] | 0.278[c] |
| CHFS | 0.422[a] | 0.350[b] | 0.344[b] | 0.356[b] | 0.243[c] | 0.200 |
| QDASH | 0.617[a] | 0.595[a] | 0.589[a] | 0.599[a] | 0.492[b] | 0.303[b] |
| VAS-overall (sHAQ) | 0.469[a] | 0.458[a] | 0.492[a] | 0.503[a] | 0.338[b] | 0.308[b] |
| VAS-Raynaud (sHAQ) | 0.330[b] | 0.336[b] | 0.354[b] | 0.365[b] | 0.252[c] | 0.309[b] |
| VAS-pain (HAQ) | 0.515[a] | 0.526[a] | 0.548[a] | 0.562[a] | 0.400[b] | 0.313[b] |
| VAS-joint pain | 0.640[a] | 0.680[a] | 0.711[a] | 0.716[a] | 0.484[b] | 0.467[b] |
| VAS-fatigue | 0.476[a] | 0.456[a] | 0.488[a] | 0.502[a] | 0.354[b] | 0.312[b] |
| SF36 PCS | −0.578[a] | −0.565[a] | −0.568[a] | −0.583[a] | −0.437[b] | −0.351[b] |
| SF36 MCS | −0.192 | −0.193 | −0.255[c] | −0.243[c] | −0.126 | −0.090 |

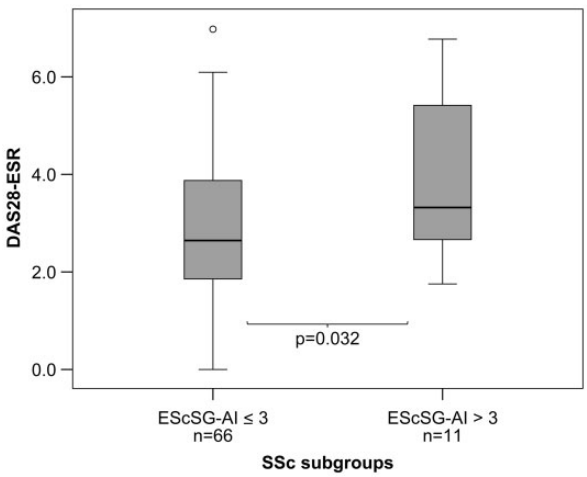
Spearman correlation coefficients are displayed in the table. [a]Correlation is significant at the 0.001 level (two-tailed). [b]Correlation is significant at the 0.01 level (two-tailed). [c]Correlation is significant at the 0.05 level (two-tailed) VAS: visual analogue scale; sHAQ: Scleroderma Health Assessment Questionnaire; SF36 PCS: Short Form Health Survey Physical Component Scale; SF36 MCS: Short Form Health Survey Mental Component Scale; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; QDASH: Quick Questionnaire of the Disability of the Hands, Arms and Shoulders; MSAI: Modified Scleroderma Disease Activity Index; CHFS: Cochin Hand Function Scale; EScSG-AI: European Scleroderma Study Group Activity Index; DAS28-ESR: DAS of 28 Joints using ESR; DAS28-CRP: DAS of 28 Joints using CRP.

**Fig. 2** Boxplot displaying discriminant validity of DAS28-ESR by comparing SSc to control groups




PRP: primary Raynaud's syndrome, HC: healthy control, DAS28-ESR: DAS of 28 Joints using ESR, P: significance of the Mann-Whitney U-test comparing the two groups.

**Fig. 3** Boxplot displaying discriminant validity of DAS28-ESR by comparing SSc subgroups based on disease activity




EScSG-AI: European Scleroderma Study Group Activity Index, DAS28-ESR: DAS of 28 Joints using ESR, P: significance of the Mann-Whitney U-test comparing the two subgroups.

reliability of DAS28-ESR, DAS28-CRP, SDAI and CDAI was 0.98, 0.97, 0.92, 0.92, Cronbach $\alpha$ was 0.99, 0.98, 0.96, 0.96, respectively ($P < 0.001$). Each assessment lasted 3–5 min.

### Comparison with the eight joint counts

Similarly to the DAIs in question, the 8JTC and 8JSC showed significant correlation with measures of disease activity (EScSG-AI, MSAI and VAS-physician) and with measures of disability (HAQ, CHFS, qDASH, VAS-overall) (Table 3). However, the 8JTC did not discriminate between patients with SSc and PRP (Table 2). Moreover, 8JTC failed to discriminate SSc patients with an EScSG-AI score higher than 3 (n = 11) and patients with an EScSG-AI score of 3 or less (n = 66), while 8JSC did not discriminate between SSc patients with HAQ <1 and those with HAQ ⩾1 (data not shown). Neither 8JTC, nor 8JSC distinguished between subgroups of SSc patients with high and low inflammatory markers (CRP (⩽5 *vs* >5 mg/l) and ESR (⩽30 *vs* >30 mm/h).

## Discussion

Our results indicate that DAS28-ESR, DAS28-CRP, SDAI and CDAI composite scores are valid measures for the assessment of arthritis in SSc. As observed in RA, the more simple indices (CDAI and SDAI) showed a very similar performance to the DAS28-ESR and the DAS28-CRP, and the four DAIs highly correlated with each other [41]. The strength of correlation between each DAI and HAQ (r = 0.48–0.50) in the SSc patients corresponded with previous data in RA [6].

Articular tenderness was a frequent finding in SSc (Table 1 and Fig. 1). All four investigated DAIs showed strong correlation with pain, and particularly strong with joint pain (Table 2). The other potential sources of pain including skin ulcers did not influence the results. No significant difference was found in the values of articular indices of subgroups based on the presence or absence of skin ulcers, and subcutaneous calcinosis (data not shown).

Irreversible damage did not influence the values of DAS28-ESR, DAS28-CRP, SDAI and CDAI in SSc. In this study no correlation was found between the scores of articular indices and the measures representing mainly structural damage, such as HAI, deltaFTP and CC28. Moreover, disease duration and age did not show any correlation with the articular DAIs either, which also support that these indices rather represent articular disease activity of SSc, than articular damage.

High prevalence of DIP involvement (20–72%) was exhibited by radiographic methods, as X-ray, US or MRI in previous reports [43, 44]. In this study physical examination of the SSc patients did not demonstrate a higher prevalence of tenderness or swelling in the DIP joints compared with patients with RA. There seems to be no need for supplementing the 28 joint counts with the DIPs in SSc (Fig. 1). However, radiologic investigations concerning this matter are warranted. It must also be noted that in other diseases, such as PsA, the 68/66 joint counts were found more reliable, than the 28 joint counts [45].

Face validity of the DAIs in SSc was proved by the presence of synovitis—characterized by joint tenderness and/or swelling; the strong association found between elevated levels of acute phase reactants and the presence of synovitis and; presence of radiographic joint changes similar to that seen in RA [11, 14, 46]. Construct validity of the articular DAIs was established by significant correlations with measures of disease activity [EScSG-AI, MSAI, VAS-physician, VAS-overall (sHAQ), CRP, ESR]. SSc is a multidimensional disease, where global disease activity can be represented by various features (skin, lung, heart, vascular and musculoskeletal involvement).

The DAIs also significantly correlated with measures of functional ability (HAQ, DASH, CHFS) and physical health related quality of life (SF36-PCS). DASH and CHFS are measures of functional ability of upper extremities, while HAQ has been shown to account for hand involvement in 75% [47]. The high correlation of the articular indices with these three measures can be explained by the fact, that the majority of the joints assessed in the 28 joint count refer to the upper limb. The floor and ceiling effects were not present at either of the articular DAIs, and all four DAIs represented disease activity and joint involvement; but not structural damage according to the principal component analysis. This means content validity was demonstrated for all four DAIs. The investigated indices also have structural validity because they were found to be unidimensional.

All four indices were able to discriminate between SSc and RA patients, SSc and PRP, SSc and healthy controls. DAS28-ESR, CDAI and SDAI scores were able to discriminate between SSc subgroups, and active *vs* inactive disease based on EScSG-AI results, while DAS28-CRP failed this test. All four indices were able to discriminate between SSc patients with and without significant disability according to HAQ. Regarding reliability, the DAS28-ESR performed best among the four indices, however good interobserver and intraobserver reliability was proved for all articular indices.

Feasibility was proven for all four articular indices. The joint examination and completion of the VAS-s lasted <5 min per patient. Additional training is not required for rheumatologists experienced in the assessment of RA patients.

Though the 8JTC and 8JSC showed similarly strong correlation with measures of disease activity and disability as the investigated four DAIs, their discriminative ability concerning SSc and negative controls, as well as discriminating between subgroups of SSc based on parameters of disease activity was poor. Thus, these more simple measures seem less appropriate outcomes for SSc, than the DAIs using 28 joint counts.

In this study DAS28-ESR showed the best results regarding construct validity, discrimination and reliability. However, the better performance of DAS28-ESR compared with DAS28-CRP might be explained by the presence of ESR and absence of CRP in the item list of EScSG-AI. In the context of outpatient care, where

prompt laboratory results are not available, CDAI can be used.

Our study has some limitations: a relatively high number of patients did not have tender or swollen joints; and further study is needed to assess the articular DAIs regarding sensitivity to change, predictive value and cut-offs for the active, moderately active arthritis and remission of arthritis in SSc.

Avouac *et al.* [14] found strong association between synovitis, joint contractures and tendon friction rubs in multivariate analysis, and reported that contractures develop during the first couple of years of the disease. This was confirmed by our previous and also our current findings, as the number of contractures did not differ in SSc patients with disease duration of 4 years or less compared with those with longer disease duration [9]. Early pharmacologic treatment and follow up of articular disease activity using DAIs might prevent the development of joint contractures in patients with SSc [11]. However, so far there is no evidence based therapy for arthritis and prevention of joint contractures in SSc, only some reassuring observations are recently available [27, 44]. Therapeutic approach is mainly based on experience gained in RA. Randomized controlled clinical trials focusing on the treatment of joint involvement in SSc are highly warranted [44].

In summary, all investigated DAIs can be used in clinical trials and later on they might also be used in daily clinical practice for assessing articular disease activity in SSc patients.

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# A Cochin kézfunkciót felmérő teszt Magyarországra történő adaptálása és validálása szisztémás sclerosisos, valamint rheumatoid arthritises betegeknél

**Varjú Cecília dr., Gulyás Katinka dr., Farkas Nelli dr., Kárpáti Eszter dr., Lóránd Veronika dr., Czirják László dr.**

Pécsi Tudományegyetem, Pécs

**A szisztémás sclerosis (SSc) és a rheumatoid arthitis (RA) a kézfunkció súlyos károsodásával járó reumatológiai kórképek. A kézfunkció felmérésére önkitöltős kérdőívek alkalmazása egyszerű, bevált módszer.**

**A tanulmány célkitűzése a nemzetközileg elterjedt Cochin kézfunkciót felmérő kérdőív Magyarországra történő adaptációja és validálása volt reumatológiai betegeken.**

**A szerzők a Cochin-teszt magyarra lefordítását követően 40 SSc-s, 34 RA-es és 21 fő egészséges kontroll kérdőíves felmérését, pszichometriai és statisztikai elemzését végezték el.**

**A Cochin-teszt, a Health Assessment Questionnaire egészségfelmérő kérdőív és a Hand Anatomic Index (kézanatómiai index) eredményei szoros összefüggést mutattak, együtt mozogtak. Az egészséges csoporthoz képest a RA-es ($p<0,001$) és a SSc-os ($p<0,05$) csoportoknál jelentős különbség mutatkozott a kézfunkcióban, míg a SSc-osok és a RA-esek között a tesztek nem mutattak szignifikáns különbséget. A reprodukálhatóság tekintetében az intraklassz korrelációs együttható magas volt.**

**A Cochin-teszt Magyarországra történő adaptációja, validálása sikeresnek tekinthető. A Cochin-teszt gyors, egyszerű és jól differenciáló módszer a kézfunkció felmérésében.**

**KULCSSZAVAK: szisztémás sclerosis, rheumatoid arthritis, kézfunkciót felmérő kérdőív, Health Assessment Questionnaire, Cochin kézfunkciót felmérő teszt, kérdőívvalidálás**

**THE ADAPTATION AND VALIDATION OF THE COCHIN HAND FUNCTION SCALE TO HUNGARY FOR PATIENTS WITH SYSTEMIC SCLEROSIS AND RHEUMATOID ARTHRITIS**

**Systemic sclerosis (SSc) and rheumatoid arthritis (RA) often cause severe impairment of the hand functions. Questionnaires filled out by the patients are simple and practical methods in the assessment of the hand functions.**

**The objective of this study was to adapt and to validate the internationally used Cochin hand function scale to Hungary in rheumatic patients.**

**Following the Hungarian translation of the Cochin test, 40 SSc, 34 RA patients and 21 healthy control persons filled out the questionnaires and the psychometric and statistical analyses of those have been conducted.**

**The results of the Cochin test, the Health Assessment Questionnaire and the Hand Anatomic Index showed a close correlation and moved together. A significant difference appeared regarding the hand function in both the RA and the SSc groups compared to the healthy patients, while the tests did not show a significant difference between those in the RA and those in the SSc group. Regarding test-retest reliability the Cochin scale showed a high intraclass correlation coefficient.**

**The Cochin scale was successfully validated and adapted to the Hungarian setting. The Cochin test is a simple and useful method recommended for the investigation of hand function in rheumatic diseases including RA and SSc.**

**KEYWORDS: Systemic sclerosis, Rheumatoid arthritis, Hand function test, Cochin Hand Function Scale, Duruöz Hand Index, Health Assessment Questionnaire, Questionnaire validation,**

## Bevezetés

A szisztémás sclerosis (SSc) a bőr, a mozgásszervek és a belső szervek érintettségével járó autoimmun betegség, melynek fő patológiai jellemzői az autoimmun gyulladás, a fokozott fibrózisra való hajlam, a generalizált artériás obliteratív vasculopathia és a következményes, több szervrendszert, így a mozgásszerveket is érintő atrófia [1–3]. A SSc-nak két fő formáját különítjük el, a diffúz cutan szisztémás sclerosist (dcSSc) és a limitált cutan szisztémás sclerosist (lcSSc). A mozgásszervek érintettsége mindkét formában előfordul, és nagymértékben befolyásolja a betegek életminőségét [4–7]. A SSc leggyakoribb mozgásszervi tünete a kézízületi polyathralgia/polyarthritis, mely az irodalmi adatok szerint 46–97%-ban van jelen. SSc-ban kezdeti tünetként a Raynaud-szindróma mellett a betegek kézízületi fájdalmai hátterében az inakat és az ízületeket finoman destruáló, erozív ízületi gyulladás (synovitis és/vagy tenosynovitis) áll fenn, amely finomabb felbontású képalkotó vizsgálatokkal kimutatható, hamar az ízületi rés beszűküléséhez és változóan súlyos kontraktúrák kialakulásához vezet. A dcSSc-ban ritkán tapintható ínhüvely-crepitatio rosszabb prognózist jelez. Ízületi kontraktúra leggyakrabban a kézen, jellemzően a metacarpophalan-

gealis (MCP), a csukló, a proximális (PIP) és a distalis interphalangealis (DIP) ízületekben alakul ki. Az MCP ízületi sorban jellemzően extenziós, a PIP- és DIP-ízületekben flexiós kontraktúra (súlyos esetben ún. karomállás) alakul ki, míg a hüvelykujj addukciós, a csukló pedig semleges pozícióba kerül. A tapintható synovitissel járó polyarthritis ritka tünet, míg a polyarthralgia-polyarthritis gyakrabban figyelhető meg. A legújabb kezelési protokollok SSc esetében is a korai arthritisek hatékonyabb, ún. betegségmódosító (DMARD) szerekkel történő kezelését javasolják [4–6]. SSc-ban a kézízületek funkcióját szintén rontja a leggyakrabban itt megjelenő subcutan calcinosis, az ujjbegyeken kialakuló ischaemia vagy kalciumlerakódás okozta bőrfekélyek és a végpercek csontjának gyakori resorptiója. A kezek funkcionális károsodása a rheumatoid arthritisben (RA) jellemzővel hasonló mértékű, ezenfelül a tüdő és más belső szervi bajok mellett a kézfunkció károsodása döntő mértékben rontja a betegek életminőségét. A kezeken kívül, főleg súlyosabb SSc-os betegeken, előfordul a könyökök, vállak, térdek, bokák és a láb kisízületeinek érintettsége is. Proximális izomgyengeség (főleg a váll és a csípő területén), kreatin kináz szérumszint-emelkedés szintén előfordul SSc-ban [1, 4–6].

A RA a végtagízületek progresszív gyulladásával járó reumatológiai betegség, amely elsősorban az ízületek irreverzibilis destrukciójához vezet [8–10]. A kórképre jellemző, hogy kezdetben a gyulladás szimmetrikusan főként a kéz kisízületeit érinti, amely kezelés nélkül súlyos kézfunkciós károsodást okoz. Legelőször általában a csukló ízületei, az MCP- és PIP-ízületek betegszenek meg, míg a DIP-ízületsor végig megkímélt. A krónikus betegség során a porcés a csonteróziói mellett az ízületi tokok zsugorodnak, megváltozik az inak ízületekhez viszonyított helyzete, vagy a csontok resorptiója is létrejöhet, következményesen a betegségre jellemző ízületi subluxatiók alakulnak ki. Az MCP-ízületekben gyakran ulnaris irányú deviatio állandósul, míg a hüvelykujj ízületi károsodása az I. MCP addukcióját és az IP hyperextenzióját okozza. A kézujjakon a RA-re jellemzően ún. „gomblyukdeformitás" a PIP-ízület flexiós és a DIP-ízületi extenziós kontraktúrája – vagy „hattyúnyak-deformitás"- a PIP hyperextenziós és a DIP-ízület flexiós kontraktúrája is kialakulhat. A RA-ben a nagyízületek és a nyaki gerinc is részt vesznek a gyulladásos folyamatban, amely összességében a beteg súlyos mozgáskorlátozottságát okozza [9, 10].

A kézízületek károsodásának felmérésére, követésére több módszer áll rendelkezésre, például az ízületek mozgásterjedelmének mérése ízületi szögmérővel, ami lassú és a többszörös kontraktúrák miatt RA-ben és SSc-ban is nehezen kivitelezhető, és alig reprodukálható módszer. Helyette SSc-os betegeknél az ujjbegy–tenyér távolság rendszeres mérése a Delta-fingertip to palm index (Delta-FTP) alkalmazása [11] vagy RA-ben és SSc-ban is a Hand Anatomic Index (HAI) [12, 13] kiszámolása egyszerűbb és validált módszer. A Delta-FTP mérése a III. ujj sugarában történik: az ujjbegy felső pontjától a distalis tenyérredőre eső pontig való távolság különbsége kinyújtott kéz és maximálisan a distalis tenyérredőhöz behajlított II–V. ujjak mellett. A HAI-érték az I. és az V. ujjbegy terpesztett és zárt távolságának különbsége elosztva az MCP-ízületsor asztallaptól számított maximális oldalmagasságával képlettel határozható meg.

A RA-es betegek gyulladásos aktivitása szorosan összefügg a testszerte összeszámolható, gyulladásban lévő ízületek számával. A nemzetközileg validált és a mindennapi gyakorlatban alkalmazott Disease Activity Score 28 (DAS28) 28 meghatározott ízület (ezen belül 22 kézízület) sinovitisének vizsgálatával kiváló mutatója a kézízületi gyulladás státusának [14].

A kézfunkció vizsgálata SSc-ban és RA-ben a beteg által kitölthető kérdőíves módszerrel történik [15, 16], vagy meghatározott kézfunkciókat felmérő feladatok elvégzésének képességét (performance tesztek) [17, 18] értékelik. Jelenleg a magyarországi kultúrához általunk adaptált felső végtagi funkciót felmérő kérdőívek közül a Disabilities of the Arm, Shoulder and Hand (DASH), a kar-, a váll- és a kézízületek funkcióját felmérő teszt [19], valamint a Health Assessment Questionnaire (HAQ) [20–22], általános funkciót felmérő teszt elérhető. A HAQ-teszt a legelterjedtebb funkciót felmérő teszt a reumatológiai gyakorlatban, amely 60%-ban a kéz funkciójával kapcsolatos kérdéseket tesz fel, így számos korábbi tanulmány kimutatta, hogy a HAQ–fogyatékossági mutató (HAQ–DI) szorosan összefügg a kéz funkcionális képességével.

Jelen tanulmányunkban a reumatológiában egyre szélesebb körben alkalmazott, 1996-ban a párizsi Cochin kórházban dolgozó *Duruöz és mtsai* által összeállított Cochin kézfunkciót felmérő teszt (Cochin hand function scale, más néven Duruöz hand index) *(1. melléklet)* magyarra történő lefordítását és a helyi kultúrához való adaptálását, valamint reumatológiai betegeken statisztikai, ún. pszichometriai módszerrel történő kipróbálását (validálását) végeztük el [23–29]. A Cochin-teszt alkalmazása fontos, mert várhatóan pontosabban mutatja a kézfunkció finomabb károsodását és változását. A vizsgálatban SSc-os, RA-es betegek és egy egészséges kontrollcsoport kézfunkcióját hasonlítottuk össze fizikális vizsgálat és különböző tesztek segítségével.

## Betegek és módszer

Betegeink vizsgálata a PTE KK Reumatológiai és Immunológiai Klinikán 2011. októbertől 2012. júliusig zajlott. A vizsgálatban összesen 95 fő vett részt: 40 SSc-os, ebből 18 lcSSc-os nőbeteg, az átlagéletkoruk 60,8±13,6 év, 22 dcSSc-os beteg (19 nő, 3 férfi), átlagéletkoruk 55,8±12,3 év, 34 RA-es beteg (25 nő, 9 férfi), átlagéletkoruk 57,7±12,5 év, valamint további 21 egészséges személy, (20 nő és 1 férfi) átlagéletkoruk 58,6±11,7 év, ők a kontrollcsoportot alkották.

A betegek vizsgálata során 28 ízület állapotát kísértük figyelemmel, rögzítettük a betegek nyomásra érzékeny és

duzzadt ízületeinek számát. Vizsgáltuk mindkét kéz MCP- és PIP-ízületeit, valamint a csukló-, a könyök-, a váll- és a térdízületeket, meghatároztuk a DAS28-értéket, majd a HAI- és a Delta-FTP-tesztek értékeit. Az újonnan adaptált Cochin-kéztesztен kívül a korábban már validált HAQ-kérdőívet és egy ehhez kapcsolódó fájdalom-vizuális analóg skálát (Fájdalom-VAS) is kitöltettük a vizsgálatban részt vevőkkel. A betegek kórtörténetéből kigyűjtöttük az egy hónapon belül kapott szérum C-reaktív protein- (CRP) szint és vörösvértest-süllyedés (We) értékeket.
A vizsgálatban részt vevők valamennyien tájékoztatást kaptak a tanulmány céljáról, módszereiről, következményeiről majd aláírásukkal igazolták, hogy a vizsgálatban önkéntesen vesznek részt. A vizsgálat menetét a Regionális Etikai Bizottság jóváhagyta (2720/2006).

## A Cochin kézfunkciós teszt

A Cochin-tesztet *(1. melléklet)* eredetileg RA-es betegek kézfunkciójának gyors felmérésére szerkesztették és validálták, majd néhány éven belül osteoarthritises és SSc-os betegeken is sikeresen alkalmazták és validálták [23–28]. A 18 kérdésből álló kérdőív a mindennapi élettel kapcsolatos tevékenységekre vonatkozó kérdéseket tartalmaz. A kérdések öt kérdéskörre bonthatók: az étkezéssel, az öltözködéssel, a higiéniával kapcsolatos, valamint az irodai és az egyéb tevékenységekkel összefüggő témakörökre. Csoportosíthatók a kérdések annak alapján is, hogy milyen típusú kézmozgás szükséges az elvégzésükhöz. Így három alcsoportot különböztetünk meg. Az elsőbe tartoznak az erőt és rotációs kézmozgást igénylő tevékenységekre vonatkozó kérdések, a másodikba a kézügyességgel és precíz mozdulatokkal kapcsolatos kérdések, a harmadikba pedig a domináns kéz első kettő, illetve első három ujjával végrehajtott szorító mozgásokra vonatkozó kérdések [23–24]. A kérdőív kérdéseire a hatféle válasznak megfelelően 0–5 közötti értéket rendelünk: a legjobb funkcióhoz tartozó érték a 0 pont, amikor nehézség nélkül sikerül, míg a legrosszabb érték az 5 pont, amikor lehetetlen a beteg számára elvégezni a kérdezett feladatot. A kérdőív kitöltése 3–5 percet vesz igénybe. A tesztérték kiszámolása úgy történik, hogy a 18 kérdésre adott válasz értékeit összeadjuk, így a legalacsonyabb a 0, a legmagasabb pedig a 90 pont lehet.

*A Cochin-teszt Magyarországra történő adaptálása*
A Cochin-tesztben szereplő 18 kérdés és válasz angolról magyar nyelvre fordítását és a magyar kultúrához adaptált kérdőív validálását a nemzetközileg elterjedt ún. „oda-vissza fordítási módszerrel" végeztük el [30], ahol az első lépésben két orvoskolléga és két, nem az egészségügyben dolgozó („nem informált") angol nyelvet oktató tanár fordította le a kérdéseket angolról magyarra. Ezt követően egy szakértői csoport: egy orvos, egy orvostanhallgató, egy diplomás gyógytornász, egy nyelvész és két felkért sclerodermás beteg közösen megalkotta a kérdőív első magyar változatát, melyet ezután két független, „nem informált" angol anyanyelvű, de hosszú ideje Magyarországon élő segítő visszafordított angol nyelvre. Összehasonlítva az újra angolra fordított tesztet és az eredetit, nem volt lényeges jelentésbeli különbség. Ezután a korábbi szakértői csoport véglegesítette a Cochin-teszt magyar változatát.

Kérjük jelölje X-szel a jelen állapotára jellemző megfelelő választ!

| Képes-e... | nehézség nélkül | kis nehézséggel | közepes nehézséggel | nagy nehézséggel | szinte lehetetlen megcsinálni | lehetetlen megcsinálni |
|---|---|---|---|---|---|---|
| 1. ...megtartani egy tálat? | | | | | | |
| 2. ...megfogni és felemelni egy tele üveget? | | | | | | |
| 3. ...megtartani egy tányért tele étellel? | | | | | | |
| 4. ...folyadékot önteni üvegből pohárba? | | | | | | |
| 5. ...lecsavarni egy előzőleg már kinyitott konzervüveg tetejét? | | | | | | |
| 6. ...húst vágni késsel? | | | | | | |
| 7. ...felszúrni dolgokat villával? | | | | | | |
| 8. ...gyümölcsöt hámozni? | | | | | | |
| 9. ...begombolni az ingét? | | | | | | |
| 10. ...fel- és lehúzni a cipzárt? | | | | | | |
| 11. ...megnyomni egy új tubus fogkrémet? | | | | | | |
| 12. ...jól megfogni egy fogkefét? | | | | | | |
| 13. ...egy átlagos tollal leírni egy rövid mondatot? | | | | | | |
| 14. ...megírni tollal egy levelet? | | | | | | |
| 15. ...elfordítani az ajtógombot? | | | | | | |
| 16. ...ollóval papírt vágni? | | | | | | |
| 17. ...felvenni érméket az asztalról? | | | | | | |
| 18. ...elfordítani a kulcsot a zárban? | | | | | | |

**1. melléklet. A Cochin-kézfunkciót felmérő teszt magyar változata**

*Validálás, pszichometriai statisztikai értékelés, szakmai hitelességi elemzés*
Munkánkban a reumatológiai kórképekre kidolgozott, ún. „OMERACT filter" néven közzétett validálási módszertani ajánlást követtük [30–33].

*Tartalmi hitelesség* (content validity)
A megjelölhető válaszok skálájának hitelességét a „padló és plafon effektus" („floor and ceiling effect") vizsgálattal végeztük el. A kérdésekre adott válaszok között a „plafon effektus", azaz a lehető legjobb funkcionális állapotot jelentő nulla pontszám elért aránya és a „padló effektus", azaz a lehető legrosszabb állapotot jelentő maximális tesztpontszám 15% feletti aránya nemkívánatos, mert ez esetben a mérésre használt skála nem a vizsgált betegcsoport által adott válaszoknak megfelelő tartományban helyezkedik el [30].

*Szerkezeti hitelesség* („structure validity")
A szerkezeti megbízhatóság vizsgálatára a faktorelemzés egyik formáját, a főkomponens elemzést (ortogonális forgatással) alkalmaztuk. A módszer lényege, hogy a Cochin-teszt egyes kérdései korrelációs együtthatóinak elemzése alapján a kérdéseket csoportokba, más néven dimenziókba, főkomponensekbe rendezze, ezzel könnyítve, egyszerűsítve a további statisztikai elemzést. A korábbi Cochin-teszt-validálásról olvasott szakirodalmi adatok alapján a kérdések kettő vagy három főkomponensbe tömörülését vártuk [22, 30–31].

*Megegyezési hitelesség* („concurrent/ convergent/ criterion validity")
A Cochin-teszt validálásához viszonyítási alapként hasonló jellegű, már validált önkitöltős tesztet, a HAQ-tesztet és a Fájdalom-VAS mutatót, valamint a fizikális vizsgálat értékeit, így a HAI- és Delta-FTP-teszteket használtuk.

*Diszkriminatív hitelesség* („discriminant validity")
A Cochin-teszt-értéknek azt a képességét vizsgáltuk, hogy mennyire tud különböző súlyosságú kézfunkció-károsodások közötti különbségeket kimutatni. Mann-Whitney U-teszttel vizsgáltuk, hogy a különböző kézkárosodással jellemezhető (súlyosabb és kevésbé súlyos állapotú) SSc-os, RA-es és egészséges kontroll vizsgálati csoportok esetében mennyire mutat eltérést a Cochin-teszt értéke [30–31].

*Megbízhatóság – belső konzisztencia* („internal consistency") és *reprodukálhatóság* („test-retest reliability")
A kérdőív egyes kérdéseire adott válaszok belső konzisztenciájának a vizsgálatát a Cronbach-alfa mutató számolásával értékeltük, a domainek egyenkénti kihagyásakor az adatok konzisztenciájának a jelentős növekedésére nem számítottunk.

A reprodukálhatóságot egymás után két alkalommal, átlagosan egy hét elteltével ismételten kitöltött Cochin-teszt eredményéből intraklassz korrelációs koefficiens kiszámításával határoztuk meg. Feltételeztük, hogy a kérdőívek ismételt kitöltése idejéig a betegek állapota változatlan maradt [30–31].

## Eredmények

*A Cochin-teszt validálása*
A Cochin-teszt magyarországi kulturális adaptálását próbatesztek kitöltését követően végeztük el. Betegeink által meggyőződtünk a teszt érthetőségéről, és miután nem javasoltak módosítást, véglegesítettük annak magyar nyelvű kérdéseit.

A betegek a Cochin-tesztet átlagosan 2 perc 40 mp alatt töltötték ki.

A validálási vizsgálatban részt vevők által kitöltött kérdőívek és a betegek gyulladását jelző laboratóriumi eredményeit az *I. táblázat*ban foglaltuk össze.

| Tesztek (ponthatárok) | Kontroll n=21 | RA n= 34 | SSc n=40 | lcSSc n=18 | dcSSc n=22 |
|---|---|---|---|---|---|
| Cochin-teszt (0-90) | 5 (1,0–8,0) | 19** (8,3–36,3) | 14* (3–26,8) | 7 (2,5–24,5) | 15,5** (4.5–31) |
| HAQ-DI(0-3) | 0,25 (0–0,5) | 1,5** (0,9–2,1) | 1,3** (0,7–1,8) | 1,1* (0,25–1,9) | 1,5** (0,7–1,75) |
| Fájdalom-VAS (0-100) | 15 (3–28) | 50** (27,5–75) | 34** (20–57) | 42,5* (14–62) | 30* (20–53) |
| DAS28 | – | 4,14 (3,0–5,7) | 3,4 (2,5–4,3) | 3,5 (2,7–5,4) | 3,2 (2,4–3,6) |
| HAI jobb | – | 2,1 (1,3–2,6) | 1,8 (1,3–2,3) | 1,95 (1,4–2,3) | 1,55 (1,3–2,4) |
| Delta-FTP | – | – | 7,0 (5,2–8,9) | 7,9 (6,4–9,6) | 6,35 (4,2–8,8) |
| We (mm/h) | – | 21,5±18,9 | 22,6±18,8 | 29,7±24,2 | 16,9±10,3 |
| CRP(mg/l) | – | – | 5,4±5,8 | 7,1±6,6 | 3,9±4,7 |

A táblázatban a medián és IQR, valamint átlag és szórás (±SD) értékeket tüntettük fel.
HAQ-DI: Health assessment questionnaire disability index [20], Fájdalom-VAS: fájdalmat mérő vizuális analóg skála 100 mm-es, DAS28: Disease Activity Score 28 ízületen [14], HAI: Hand Anatomic Index/kézanatómiai index [13], Delta-FTP: delta ujjbegy-tenyér távolság [11], CRP: C-reaktív protein.
*p<0,05, ** p<0,01 (Mann-Whitney U-próba számítás a kontrollcsoporthoz viszonyítva történt, diszkriminatív hitelesség számítás)

**I. táblázat. 40 szisztémás sclerosisos (SSc), 34 rheumatoid arthritises (RA) beteg és 21 egészséges kontroll fizikális, kérdőíves és laboratóriumi vizsgálatának eredményei**

| | 40 Ssc-os beteg<br>Cochin-teszt pontszám | 34 RA-es beteg<br>Cochin-teszt pontszám |
|---|---|---|
| Életkor | Nem szignifikáns | rho= 0,400, p<0,05 |
| HAQ-DI | rho= 0,709, p<0,001 | rho= 0,831, p<0,001 |
| DAS28 | rho= 0,454, p<0,01 | rho= 0,471, p<0,01 |
| HAI jobb oldal | rho= –0,512, p<0,01 | rho= –0,376, p<0,05 |
| Delta-FTP jobb oldal | rho= –0,649, p<0,001 | nincs adat |
| Fájdalom-VAS | rho= 0,624, p<0,001 | rho= 0,365, p<0,05 |
| Vörösvértest-süllyedés | Nem szignifikáns | Nem szignifikáns |
| C-reaktív protein | Nem szignifikáns | nincs adat |

rho=Spearman-féle rangkorrelációs együttható, HAQ-DI: Health Assessment Questionnaire Disability Index [20], DAS28: Disease Activity Score 28 ízületen [14], HAI: Hand Anatomic Index/kézanatómiai index [13], Delta-FTP: Delta-ujjbegy-tenyér távolság [11], Fájdalom-VAS: fájdalmat mérő vizuális analóg skála 100 mm-es.

**II. táblázat. Megegyezési hitelesség vizsgálat. 40 szisztémás sclerosisos (SSc), 34 rheumatoid arthritises (RA) beteg Cochin-teszt és korábban már validált tesztek, valamint laboratóriumi eredmények Spearman-féle rangkorrelációs analízissel kapott összefüggései**

*Tartalmi hitelesség*

A „padló és plafon effektus" vizsgálata során a Cochin-teszttel legjobb funkcionális állapotot (0 pont) SSc-s betegeknél 5-en (13%), az RA-s betegeknél 4-en (12%) értek el, míg maximális, 90 pontot, azaz a lehető legrosszabb értéket egyik betegcsoportban sem mértünk.

*Szerkezeti hitelesség*

A főkomponens-elemzés során a kérdések két fő komponensbe történő csoportosulását kaptuk. Az első dimenzióba tartoznak az erőt és rotációs kézmozgást igénylő tevékenységekre vonatkozó (1., 2., 3., 4., 7., 9., 10., 11., 12., 15., 18. kérdés), míg a másodikba a kézügyességgel és precíz mozdulatokkal kapcsolatos kérdések (5., 6., 8., 13., 14., 16., 17. kérdés).

*Megegyezési hitelesség*

Spearman-féle rangkorrelációs analízissel szignifikáns összefüggéseket találtunk a Cochin-teszt magyar változata és a HAQ-DI, valamint a kéz károsodását felmérő módszerek, a HAI és a Delta-FTP között mind az SSc-os, mind a RA-es betegek körében. Hasonlóan szignifikáns korrelációt találtunk a gyulladásos ízületi aktivitást jelző DAS28- és a Cochin-teszt pontszámok között, azonban nem volt összefüggés betegeink We, illetőleg CRP és a Cochin-teszt-értékeik között (*II. táblázat*).

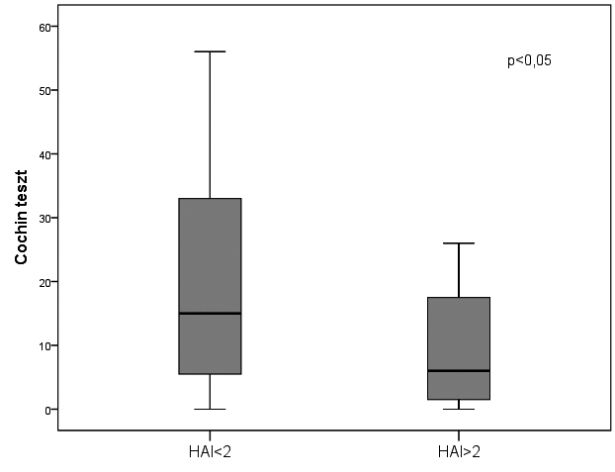
*Diszkriminatív hitelesség*

A kontrollcsoporthoz képest a RA-es (p<0,001) és a SSc-os (p<0,05) csoport esetében is jelentős különbséget mutattunk ki mind a Cochin-teszttel, mind a Fájdalom-VAS mérésekkel. Azonban a SSc-os és a RA-es betegcsoportok között a Cochin-teszt, a HAQ-DI, a Fájdalom-VAS, a DAS28 és a HAI eredmények alapján nem találtunk szignifikáns különbséget.

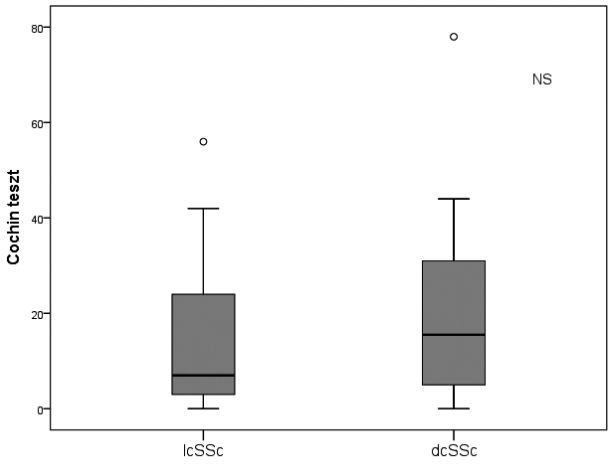
Súlyos kézkárosodást mutató SSc-os betegcsoportot (ahol a HAI<2 vagy a Delta-FTP<7 cm) hasonlítottunk össze enyhébb (ahol a HAI>2 vagy a Delta-FTP>7 cm) kézkárosodású SSc-osokkal. A két csoport között a Cochin-teszt Mann-Whitney U statisztikai módszerrel szignifikáns különbséget mutatott (*1. ábra*).

Az lcSSc-os és a dcSSc-os csoportok között azonban a Cochin-teszttel vizsgálva a kézfunkciót nem volt szignifikáns a különbség (*2. ábra*).

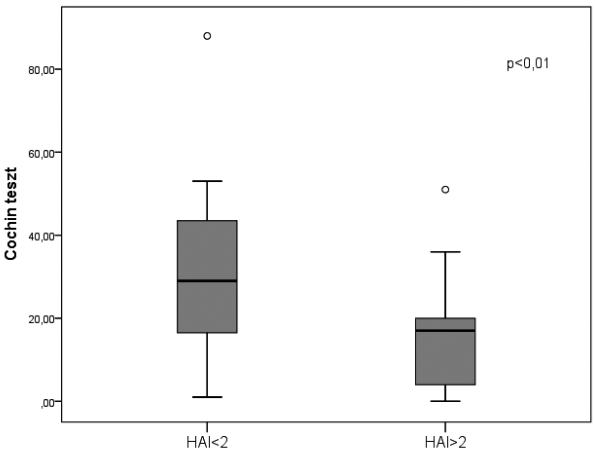
RA-es betegeknél vizsgált HAI alapján a különböző súlyosságú mozgásbeszűkülést mutató betegcsoportok között is szignifikáns különbséget találtunk a Cochin-teszt-eredmények alapján (*3. ábra*). A HAI<2 érték esetén súlyos kézkisízületi kontraktúrák figyelhetők meg, ezzel arányosan a Cochin-teszt értékei magasabbak voltak.




**1. ábra. Diszkriminatív hitelesség vizsgálat. Kéz anatómiai index alapján súlyos (n=18) (HAI<2) és nem súlyos (n=22) (HAI>2) kézfunkciójú szisztémás sclerosisos betegek Cochin-teszt-értékeinek összehasonlítása (Mann-Whitney U-teszt)**




**2. ábra. Diszkriminatív hitelesség vizsgálat. Limitált (lcSSc, n=18) és diffúz cutan szisztémás sclerosisos (dcSSc, n=22 ) betegek Cochin-teszt-értékeinek összehasonlítása (Mann-Whitney U-teszt)**




**3. ábra Diszkriminatív hitelesség vizsgálat. Kéz anatómiai index alapján súlyos (HAI<2, n=19) és nem súlyos (HAI>2, n=15) kézfunkciójú rheumatoid arthritises betegek Cochin-teszt-értékeinek összehasonlítása (Mann-Whitney U-teszt)**

*Megbízhatóság – belső konzisztencia és reprodukálhatóság vizsgálat*

A Cochin-kérdőív egyes kérdéseire adott válaszok belső konzisztenciájának vizsgálata során meghatároztuk a Cronbach-alfa értékét, ami magasnak, 0,975-nek adódott.

A SSc-os és a RA-es betegek által 5-7 nap után megismételt Cochin-kérdőív eredményei az indulási tesztértékekkel magas intraklassz korrelációs koefficiens értéket adtak, rho=0,96, p<0,001 volt.

## Megbeszélés

A Cochin kézfunkciós teszt hazai adaptációját nemzetközi standard módszer alapján végeztük. A teszt nyelvi „fordítása és visszafordítása" egyszerű volt, a betegek a próbatesztek során a kérdéseket és a válaszokat jól érthetőnek találták, további módosításokat nem javasoltak. A Cochin-tesztet a betegek többsége kevesebb mint 3 perc alatt töltötte ki.

A kitöltött tesztek eredményei alapján nem volt lényeges különbség a RA-es és a SSc-os betegek kézfunkciója között, azonban jelentős volt a különbség a kontrollcsoport és a betegcsoportok között. A korábbi tanulmányokban az SSc-osok két alcsoportja, a lcSSc-os és dcSSc-os betegek kézfunkciós tesztértékei között a Cochin- és más kézfunkciós tesztekkel változóan hol találtak [16, 18, 27], hol nem találtak [35] szignifikáns különbséget. A kéz státusát illetően mi nem találtunk a két alosztály betegeinél jelentős eltérést az elvégzett kéztesztekkel, azonban szembetűnő az általában jobb kézfunkcióval rendelkező lcSSc-os csoport vizsgálatakor rögzített nagyobb mértékű gyulladásos aktivitására utaló magasabb DAS28-, We- és CRP-értékek a dcSSc-os csoporthoz képest (*l. táblázat*).

A maximális és minimális pontszám eredmények megoszlását vizsgálva megállapítható, hogy a magyarra fordított Cochin-teszt is képes differenciálni a SSc-os és a RA-es betegek különböző funkcionális státusát.

Munkánk során a strukturális validitás vizsgálat a Cochin-teszt kétdimenziós jellegét mutatta ki főkomponens analízissel, míg az eredeti francia tanulmányban [23] ugyanezt háromdimenziósnak írták le, későbbi tanulmányokban nem találtunk erre vonatkozó adatot.

A Cochin-teszt megfelelően magas Cronbach-alfa értéke, a francia tanulmányhoz [23] hasonló, jó belső konzisztenciát jelent, tehát a megbízhatósága nem változott a Magyarországra történő adaptációját követően.

Tanulmányunkban a megegyezési validálás során a Cochin-teszt a HAQ-DI-vel mutatta a legszorosabb összefüggést mind a SSc-os, mind a RA-es betegek esetében. Hasonlóan más vizsgálatokhoz [26–29, 35], a Spearman rho-érték (0,709–0,831) igen magas volt, ami azt mutatja, hogy a kéz funkcionális állapota szoros kapcsolatban van a betegek általános funkciójával, önellátó képességével. Mindkét betegségcsoportban a Cochin-teszt szignifikáns mértékben tükrözte a kéz állapotát is az anatómiai károsodást mutató HAI-nak megfelelően. A gyulladásos aktivitással a Cochin-teszt csak részben mutatott összefüggést, mivel a polyarthritis fennállására utaló DAS28-teszttel pozitív korrelációt jelzett, azonban a We- és CRP-értékekkel a funkcionális teszt nem mutatott szignifikáns kapcsolatot.

A reprodukálhatóság tekintetében a Cochin-teszt a korábbi tanulmányokhoz [16, 23–24] hasonlóan magas intraklassz korrelációs együtthatót mutatott.

A diszkriminancia vizsgálata során megállapítottuk, hogy a különböző fokú kézkárosodás fennállása mellett a Cochin-teszttel lehetséges a különböző mértékű funkcióvesztés meghatározása.

Jelen vizsgálatunk gyenge pontja a betegek viszonylag alacsony száma, és az, hogy csak egy keresztmetszeti vizsgálat során végeztük el a Cochin-teszt magyarországi adaptálását és validálását. A továbbiakban egy követéses tanulmány elvégzését is tervezzük. Korábbi nemzetközi közleményekben már beszámoltak arról, hogy a tesztet reumatológiai betegeknél a kézfunkció követésére is sikeresen alkalmazták, és meghatározták a teszt „sensibility to change" és a „minimal important change" értékeit [28, 35–36].

Tanulmányunk értékét emeli, hogy többféle betegcsoport közreműködésével jó statisztikai eredményekkel sikerült a Cochin-tesztet Magyarországra adaptálni és részlegesen validálni.

## Összefoglalás

Eredményeink alapján a Cochin kézfunkciót felmérő teszt Magyarországra történő adaptációja sikeresnek tekinthető. A magas Cronbach-érték mutatta a magyar kérdőív csaknem változatlan belső konzisztenciáját, a megismételt tesztek közötti szoros korrelációs eredmények pedig igazolták a reprodukálhatóságot.

A Cochin önkitöltős kérdőív használata egyszerű és gyorsan kivitelezhető módszer a SSc-os és a RA-es betegek kézfunkciójának felmérésére a klinikai gyakorlatban. Különböző fokú kézkárosodás fennállása mellett a Cochin-teszt jól értékelhető funkcióvesztést mutatott.

Számításaink szerint a teszt megfelelően jól korrelál a kéz károsodásával kapcsolatos mutatókkal, és igen szoros összefüggést mutat az általános egészségi állapotot felmérő HAQ-DI-vel is, ami azt jelzi, hogy a kéz funkcionális állapota szoros kapcsolatban van a betegek általános funkcionális és önellátó képességével.

## Köszönetnyilvánítás

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Levelezés: Varjú Cecília dr., PhD., Pécsi Tudományegyetem, Klinikai Központ, Reumatológiai és Immunológiai Klinika 7632 Pécs, Akác u. 1., tel.: +36-72-536-800, fax : +36-72-536-803, e-mail: varju.cecilia@pte.hu

„A menyországért sem szabad elárulni Magyarországot."

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Quarterly Medical Review

# Musculoskeletal involvement in systemic sclerosis

Veronika Lóránd, László Czirják, Tünde Minier

University of Pécs, Faculty of Medicine, Department of Rheumatology and Immunology, 7632 Pécs, Hungary

**Correspondence:**
**Tünde Minier,** University of Pécs, Medical Center, Department of Rheumatology and Immunology, Akác u. 1, 7632 Pécs, Hungary.
minier.tunde@pte.hu

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## Summary

*Musculoskeletal (MSK) involvement is a very frequent manifestation of patients with systemic sclerosis (SSc). There are several reports about clinical trials assessing musculoskeletal involvement in SSc. However, only few controlled studies have been conducted. The prevalence of musculoskeletal symptoms, clinical and radiographic findings has been assessed. The most important articular (arthralgia, synovitis, contractures), tendon (tendon friction rubs, tenosynovitis) and muscular manifestations (myalgia, muscle weakness, myositis) should be carefully evaluated during the assessment of SSc patients, because these are not only common, but substantially influence the quality of life and some of them also have predictive value concerning disease activity and severity.*

Systemic sclerosis (SSc) is a multisystem disease characterized by vascular damage, autoimmune and fibrotic processes. Involvement of the internal organs–lungs, heart and kidney – is responsible for the high mortality of the disease. Musculoskeletal (MSK) involvement, on the other hand, is one of the main factors of the devastating disability and the dramatically decreased quality of life in scleroderma patients.
MSK involvement altogether is very common in SSc, however, there are great differences in the frequency of the various MSK manifestations. It is one of the main factors affecting quality of life in SSc. Although in different pattern and extent, it is present in both the diffuse (dSSc) and limited (lSSc) cutaneous subtypes of SSc. The MSK manifestations are listed organized by complaints, signs and symptoms below in *table I*.

## Muscle involvement

### Prevalence

The prevalence of skeletal myopathy in SSc varies from 5 to 96% due to the lack of diagnostic consensus criteria [1–11]. In the published studies most often combinations of clinical, biological,

TABLE I
**Musculoskeletal manifestations in systemic sclerosis**

| | Skeletal muscle manifestations | Skeletal manifestations | | Tendon manifestations |
|---|---|---|---|---|
| | | Articular | Non-articular | |
| Complaints | Myalgia<br>Weakness | Arthralgia<br>Joint stiffness | Shortening of digits<br>Loss of digits | Pain over the tendons |
| Symptoms | Muscle weakness<br>Muscle tenderness | Joint tenderness and/or swelling (arthritis)<br>Joint contractures | Pathological fractures | Tendon friction rubs |
| Signs (laboratory, imaging, histology) | Elevated creatin kinase and aldolase levels<br>Signs of myopathy, myositis on electromyography<br>Mononuclear inflammation, fibrosis, microangiopathy, necrosis on muscle biopsy | Elevated acute phase reactants<br>Joint space narrowing<br>Marginal erosions<br>Synovial proliferation<br>Synovial effusion | Generalized osteoporosis or osteopenia<br>Acroosteolysis and other localized bone resorption<br>Osteomyelitis | Tenosynovitis<br>Carpal tunnel syndrome |

electromyographic (EMG), MRI and/or histological evidence for muscle abnormalities were used [1,3,5,10,12–15]. Another factor of the varying prevalence may be the inclusion or exclusion of scleroderma-myositis overlap syndromes [7,16,17]. There is no consensus whether an inflammatory myopathy in SSc should rather be considered as disease symptom or as scleroderma-myositis overlap. SSc is the most common connective tissue disease associated with inflammatory myopathies, and it was found to account for 42% of patients with myositis overlap [17].

In a study by Medsger et al. [5], only 20% of patients reported muscle-related symptoms whereas upon examination, 6 (11%) had ''marked'', 10 (19%) had ''severe'', 18 (34%) had ''moderate'', and 9 (17%) had ''minimal'' weakness. Proximal muscle weakness was found in 20 of 38 patients (53%).

The role of genetic factors has not yet been systematically investigated. One Japanese study reported a prevalence of myopathy of 14% in SSc patients [13]. Afro-American scleroderma patients were found to have a higher prevalence of myositis and severe skeletal muscle involvement was also more often encountered compared to white SSc patients [18,19] and another study has shown a prevalence of 37% of myositis in black South Africans with SSc [14]. In another study, important sociodemographic, clinical, and serologic differences were found between whites, African Americans, and Hispanics, however, the frequency of myositis was not significantly different among these patient groups [20].

## Clinical symptoms

The most frequent clinical symptoms are muscle pain and weakness. The frequency of muscle pain varies from 20 to 86% [5,21] in SSc patients. Scleroderma patients with myopathy have usually symmetric proximal limb weakness that is indistinguishable from that seen in patients with idiopathic inflammatory myositis. Distal weakness may be also present [2,5] but sometimes it can be difficult to distinguish myopathic weakness from the limitation of movement due to skin sclerosis, articular changes in proximity to the assessed muscles or fibrosis of underlying tissues.

Muscle weakness reported by the treating physician was 18.9% in the lSSc and 33.5% in the dSSc subset in patients fulfilling the ACR classification criteria, and 36.5% in the ''other'' subgroup, consisting of patients with skin sclerosis distal to metacarpophalangeal (MCP) joints in the EUSTAR database comprising data of 9165 SSc patients [22]. This latter group included most probably patients with early SSc as well as cases with overlap syndromes. In other studies, the prevalence of abnormal muscle strength tested manually varied widely, from 10% up to 96% [1,5,23–25]. The lower prevalence of self-reported muscle weakness in the majority of the studies may suggest that muscle involvement in SSc patients is frequently rather mild and/or that the level of physical activity of SSc patients is reduced due to other reasons, such as malaise, synovitis, and heart or lung disease. However, in a study by Clements et al., the prevalence of self-reported muscle weakness was higher (26-40%) if compared to decreased muscle strength by manual muscle testing (MMT) (10%) [23], indicating that sometimes muscle weakness may not be due to a primary myopathy but due to other scleroderma-associated disease symptoms, such as joint involvement, skin contractures or fatigue.

Apart from the muscles of the limbs, other muscles might be also affected in SSc, e.g. head extensor muscles [7,26–28] described in several recent case reports. There are no data about the involvement of respiratory muscles in SSc, however

in patients with SSc-polymyositis/dermatomyositis overlap syndrome, respiratory muscles may also be affected [29].
Clinical association of myopathy was found with tendon friction rubs (TFR) in both SSc subsets in a recent EUSTAR study, where TFR was positively associated with muscle weakness. However, whether this was due to a generally increased disease activity or secondary due to affection of joints and tendons cannot be answered [30].
The presence of myositis was also found to be associated with myocarditis in SSc patients [4,10]. In accordance with previous studies [13,14], recent case-control studies confirmed myopathy as independent risk factor for cardiac involvement and left ventricular dysfunction in SSc [3,31]. Patients who developed cardiac disease in the aforementioned studies had more frequently inflammatory myositis with marked increase of creatine kinase (CK) levels.

## Evaluation and examination

As myopathy is relatively frequent in SSc patients and may be an early disease manifestation, all patients should be screened for muscle involvement at disease onset and regularly later on. However, it can be difficult to distinguish primary myopathic weakness from the limitation of movement due to skin thickening, articular changes in proximity to the assessed muscles or fibrosis of underlying tissues, and whether it is due to inflammation or muscle damage. Other secondary causes of myopathy are muscle weakness due to disuse (fatigue, joint involvement, pulmonary/heart involvement), atrophy because of weight loss or due to side-effects of drugs (steroids, statins, antimalarials) [32]. Therefore, when the history or physical exam (MMT) suggests the possibility of proximal muscle weakness, additional testing is indicated, including laboratory testing of muscle enzymes and respective autoantibodies, EMG, MRI and muscle biopsy.
Laboratory testing includes creatine kinase and aldolase levels, as elevation of one or both are characteristic of underlying myopathic process. However, a normal value does not exclude inflammatory myopathy, as it was demonstrated in the study by Ranque et al., where 82% of patients with biopsy proven myositis had increased CK and 76% had increased aldolase levels [21].
Several autoantibodies have been demonstrated to be associated with skeletal muscle disease in SSc patients. The anti-PM/Scl antibody was described in patients with scleroderma and polymyositis overlap. In a meta-analysis, 31% of patients with SSc and either polymyositis or dermatomyositis were anti-PM/Scl positive [33]. The PM/Scl positive patients from the Pittsburgh Scleroderma Databank had inflammatory changes on muscle biopsy in the majority of cases (58%) [34]. Other commercially available autoantibody that may be useful to identify the risk of muscle involvement in the individual patient is the anti-Ku antibody, which was associated with muscle weakness, CK elevation and myopathic EMG features compared to anti-Ku negative patients [35]. Both the PM/Scl positive and anti-Ku antibody positive SSc patients have limited cutaneous rather than diffuse scleroderma. On the contrary, the presence of anti-centromere antibody (ACA) has been found to be ''protective'' for myositis [3,4,34]. A recent EUSTAR analysis showed that in anti-Scl70 (= anti-DNA-topoisomerase I) positive patients muscle involvement occurred more often (muscle weakness in 32%, muscle atrophy in 16% and CK elevation in 8.7%) compared to ACA positive patients [9]. The presence of anti-U3-RNP (fibrillarin) was also associated with myopathy [34,36,37] in SSc patients. In a large SSc patient cohort, 4.1% of patients were found to have anti-U3-RNP positivity (38% having lSSc and 62% having dSSc). In total, 54% of anti-U3 RNP positive dSSc patients developed myositis [38]. Anti-PL7 and anti-PL12 were found to be positive in patients with myositis overlap syndromes but at a low frequency. Anti-Jo1 autoantibodies occur in scleroderma-myositis overlap syndromes in 8–24% [7,17] of patients who have myositis. Anti-SRP positivity occurs most often in ''pure'' myositis [39] and in patients with scleroderma-myositis overlap syndromes [17] and is associated with severe muscle weakness and atrophy [39].
The EMG displays pathologic findings in the vast majority of SSc patients (> 90%) [1,2,21] regardless of clinical muscle involvement, laboratory features or disease duration. The electromyographic features are similar to those of patients with polymyositis [1,2]. The overall sensitivity to detect myopathy is higher with EMG compared to MRI [21] or muscle biopsies [1,5,21,32].
The role of MRI in diagnosing muscle involvement in SSc has not been defined and up to now, there are only a few studies assessing its use in this patient cohort. In a recent study, 12 patients underwent MRI of whom 8 (67%) showed inflammation of girdle muscles with muscle atrophy and fatty infiltration in three cases [21]. Another study performed with 18 SSc patients with musculoskeletal complaints showed MRI findings compatible with myopathy or myositis in 14 (78%) patients, but no correlation was seen with the CK levels [40]. In clinical practice, MRI can be an important aid in the identification of biopsy sites.
New imaging methods for the assessment of inflammatory myopathies include contrast enhanced muscle ultrasound (US) to differentiate atrophic from inflamed muscles and specialized MR techniques such as T2 mapping, diffusion-weighted imaging and blood oxygenation level-dependent imaging, which can provide information on muscle recruitment, myofibrillar structure and can functionally evaluate the microcirculation [41,42].
The histological findings of muscle biopsies in SSc patients with myopathy are heterogeneous and non-specific. They include mononuclear inflammation, interstitial fibrosis in the

perimysium and epimysium, microangiopathy, atrophy, myofiber necrosis and regeneration of variable degree [5,6,10,21]. These histological findings were indistinguishable from patients with poly-/dermatomyositis [1,7,10, 43,44]. Only few data are available about the characterization of the cellular infiltrates in patients with SSc myopathy. In one study of 11 scleroderma muscle biopsy specimens, CD8+ and CD4+ cells were found in roughly equal proportion in perivascular cellular infiltrates, whereas CD8+ cells predominated in the perimysium [45]. In the recent study by Ranque et al., overexpression of MHC I, complement deposits on vascular walls with predominance of CD4+ T cells similar to dermatomyositis or absence of complement deposits with predominance of CD8+ cells like in polymyositis were observed [21].

One of the most important problems when assessing myopathy in SSc is the absence of definite criteria for diagnosis. At present, there is no consensus whether an inflammatory myopathy in SSc should rather be considered as disease symptom or as scleroderma-myositis overlap. Usually the myopathy is considered as being overlap when a patient with definite SSc also satisfies the published diagnostic criteria for polymyositis/dermatomyositis [46].

Clements et al. suggested two principal patterns of muscle involvement based on manual muscle strength testing, muscle enzyme levels and EMG findings [1]. The ''simple myopathy'' was a mild form that appears more frequently in SSc patients. These particular patients present with proximal muscle weakness, normal or mildly increased CK and aldolase levels, and polyphasic motor unit potentials on EMG, but without the insertional irritability and fibrillation that characterise classic polymyositis. The muscle involvement is typically refractory to corticosteroids. ''Complicated myopathy'' is far less common and represents a true overlap between scleroderma and polymyositis. This form is characterized by muscle weakness, highly increased muscle enzymes, polyphasic motor unit potentials of short duration and small amplitude, fibrillations, positive sharp waves and increased insertional irritability on EMG [1]. Several studies have supported both the presence of a rather mild form of proximal myopathy [2,25,43,44] and of myositis in patients with SSc.

However, this previously suggested classification into a simple and complicated myopathy to predict the clinical course and response to therapy may not be further sustained since an increasing number of studies do not support this classification [3–6,16,47].

When assessing the results of muscle biopsies, no clear-cut classification criteria have emerged either. However, these studies have not included immunostaining studies, therefore further assessment on the immunopathological nature of muscle involvement are needed before any new classification criteria are proposed [48].

## Prognosis

Scleroderma patients with skeletal myopathy do not seem to have worse prognosis compared to those patients without myopathy [49–51]. However, it is associated with an increased risk of myocardial involvement, which might lead to the development of late-stage late-onset life-threatening conduction defects [3,4,10,13].

## Treatment

To date, there are no generally accepted treatment recommendations regarding SSc-associated myopathy. Based on the results of retrospective studies, patients with inflammatory myopathy with elevated CK levels, inflammation on MRI or inflammatory infiltrates in muscle biopsy are treated with varying doses of corticosteroids [1,10,21] with or without immunosuppressive drugs such as methotrexate [43,44,52] whereas myopathy in patients with normal or mildly elevated CK levels and absence of inflammation on MRI or biopsy often remains untreated [1,10]. These latter patients appeared to have a relatively stable disease course even when left untreated. In SSc patients unselected for myopathy, treatment with D-penicillamine [23] or oral cyclophosphamide [52,53] had no impact on muscle involvement. A recent retrospective study of 35 SSc patients showed that corticosteroid therapy was associated with no bioclinical parameter in the multivariate analysis [21]. Distinction between good and poor responders to immunosuppressive therapy could be made only based on histopathological findings of the muscle biopsy: in patients without inflammation or necrosis on biopsy, only 13% had a favorable response to the treatment, whereas patients with necrosis, inflammation, or necrosis and inflammation on muscle biopsy had a 89%, 90%, and 100% chance of favorable treatment response. This finding was in accordance with previous studies [1,10]. However, there should be awareness for the risk of scleroderma renal crisis in patients on glucocorticoid treatment (independently of the dose used), especially in patients with early diffuse disease and poor prognostic factors [21,54,55]. High doses of corticosteroids should probably only considered in severe biopsy proven myositis [21], whereas in less severe cases, low-dose corticosteroids might be sufficient.

Regarding the use of biological therapies in SSc-associated myopathy, only a few case histories are available. In a recent study, diffuse SSc patients with progressive skin disease refractory to oral cyclophosphamide were treated with rituximab. One patient who additionally suffered from a severe myositis which did not respond to the combination of cyclophosphamide with MTX, treatment with rituximab led to the improvement of clinical symptoms and the normalization of CK levels [52]. In another study, which tested the effect of abatacept in refractory myopathy in 7 SSc patients, abatacept did not improve muscle outcome measures, although a tendency of improvement could be observed [56].

Patients with scleroderma-myositis overlap syndromes are usually treated similarly with a good response to corticosteroids in 89–100% [1,10,17,21].

### Conclusion

The skeletal muscle involvement is a relatively common manifestation in SSc. The evaluation of myopathy in SSc patients includes the testing of muscle enzymes, specific autoantibodies, manual muscle testing, EMG and muscle biopsy. With respect to autoantibodies, anti-U1-RNP, anti-U3-RNP, anti-Scl70, anti-Pm-Scl, anti-Ku, anti-Jo1 are found to be associated with myopathy in SSc and scleroderma-myositis overlap syndromes. EMG is currently probably the most reliable and sensitive diagnostic tool to detect SSc-associated myopathy. The muscle biopsy helps to identify those patients who might have beneficial therapeutic response to immunosuppressive agents. SSc patients with myopathy should be carefully screened for cardiac involvement even in the absence of cardiac complaints.

## Skeletal involvement

Skeletal involvement of the SSc can be divided into articular and non-articular involvement. Articular involvement can be present in many different forms in SSc. The most common manifestations are arthralgia and joint contractures. Arthritis is less frequent, but also relatively often present in SSc [30,57]. Joint involvement can be the initial manifestation of SSc. Its onset can be acute or insidious with an intermittent, chronic remittent, slowly progressive or rapidly progressive course which can be present in monoarticular, oligarticular, or polyarticular pattern [58]. Though involvement of the hands is more prominent and frequent in SSc than the feet, foot involvement should also be taken into consideration [59–63]. The involvement of the temporomandibular joints in SSc has also been reported in a few studies [63–65].

The main forms of non-articular involvement in SSc are generalized and localized osteoporosis, digital tuft resorption and osteolysis at other body regions.

Many studies have established an increased risk of bone loss and fracture in individuals with chronic inflammatory conditions. Patients with SSc may have an increased risk of osteoporosis (OP) because of a chronic inflammatory state, premature menopause, occult malabsorption or malnutrition, low weight, major disability, immobilization, and use of corticosteroid therapy. However, results regarding the risk of osteoporosis in SSc are still conflicting in SSc, since studies involved different SSc populations, study design, and generally a relatively small sample size [66–72]. A recent study has found that the prevalence of osteoporosis and fracture in a cohort of patients with SSc ($n$ = 71) was increased compared to the investigated healthy controls and rheumatoid arthritis (RA) control group, highlighting an increased risk of OP and fracture in SSc [73]. They have identified age and vitamin D deficiency as independent risk factors of fracture. The prevalence of OP in their SSc population was 30%. This result was in accordance with a recent review analyzing data of 19 relevant papers, where the prevalence of low bone mineral density and osteoporosis was 27%–53.3% and 3%–51.1%, respectively [74]. The prevalence of OP in women with SSc was similar to a large group of age-matched women with rheumatoid arthritis [73]. No difference in OP has been reported between patients with the limited cutaneous or diffuse cutaneous subset [70,72,73]. Corticosteroid therapy did not influence the outcome of the diagnosis of OP [73]. The similar frequency of fracture in SSc and RA population found in this particular study underlines the high risk of fracture in SSc and supports the need for systematic screening for this complication. Omair et al. also demonstrated in their recent review that patients with SSc are at risk of low BMD and fracture, especially when other risk factors for OP are present. As studies examining the risk factors for low BMD were conflicting, they suggested the need for further research for clarifying the true risk factors in SSc [74].

### Prevalence of articular involvement

Articular involvement is very common in SSc. However, only the average frequency can be estimated, partly because of the difficulties of physical examinations, partly because of the lack of consensus on assessment techniques. In the EUSTAR database frequencies of synovitis, tendon friction rubs, and joint contractures were 16%, 11%, and 31%, respectively [30].

The prevalence of arthralgia in consecutive SSc patients differs greatly, from 23 to 81%, among the studies of different institutes. However, it is mainly reported in about 70% of the patients [24,57–61,75–81].

The frequency of synovitis in SSc by clinical assessment is around 15–20% [30,58–61,75–77]. In consecutive SSc patients, the mean number of tender joints is around 3; the mean number of swollen joints is between 0 and 2 according to most studies on this issue, except for the study of Blocka et al., where this number was much higher [53,59,82–85]. According to a recent meta-analysis of 7 studies, the prevalence of radiologically detectable arthritis is 26% in SSc [86].

There is no consensus on what degree of range of motion decrease should be called a joint contracture. Therefore, the prevalence of contractures assessed by physical examination in different studies varies between 24 and 56% [23,87].

### Clinical symptoms

Synovitis can be present in patients with SSc in all disease stages, but it is most frequent in the early stage of the disease. The frequency of synovitis is higher in patients with the diffuse cutaneous subset compared to the limited cutaneous subtype, but only in early disease [30,85,88]. Arthritis-related pain is closely associated with SSc patients' health related quality of life [89]. According to Baron et al. arthritis

can be detected most often in the metacarpophalangeal joints (MCP), wrists, knees, distal interphalangeal joints (DIP), and proximal interphalangeal joints (PIP), in decreasing order [58].

Arthralgia and hand stiffness were among the four highest rated symptoms in terms of frequency and impact on daily activities in the Canadian National Survey. [57]. Arthralgia was found to be significantly more common in patients with dSSc, than with lSSc [77]. Moreover, Skare et al. reported that pain and stiffness were the symptoms that most affected functionality [81].

Contractures are one of the main sources of disability in SSc. They are frequent in both subtypes; however, the prevalence of joint contracture is higher in dSSc, than in lSSc. Moreover, diffuse cutaneous subset is an independent predictor of the progression of flexion contractures. Though the development of contractures is relatively slow and gradual, it can be present in the early stages of the disease, too [53,76,77,88,90].

## Rheumatoid arthritis-scleroderma overlap

Patients who fulfill the classification criteria of both the SSc and RA are considered as SSc–RA overlap patients. Since SSc by itself can cause significant articular damage, the determination of SSc–RA overlap is difficult. Similar changes, resembling those seen in RA, are noted in the hand joints of SSc patients [58,63]. Thus exact prevalence of true SSc–RA overlap is hard to determine, it was found in 4.6–5.2% of SSc patients [91,92]. In the study of Misra et al., 21% of the SSc patients with articular symptoms also had RA overlap [93].

Szűcs et al. reported that SSc–RA overlap patients carried the SSc-associated HLA-DR3 and HLA-DR11 alleles, as well as the RA-related HLA-DR1 and HLA-DR4 alleles in the genetic study of 22 SSc–RA overlap patients [91].

Many studies have confirmed that there is no significant difference between patients with and without erosive arthropathy on radiography in terms of rheumatoid factor (RF) [58,62,88,90]. Furthermore, synovitis detected by US does not correlate with the presence of the RF [94]. In contrast, in the study of Jinnin et al., elevated RF was seen in SSc–RA overlap patients significantly more frequently, than in those without RA [92].

Anti-CCP antibodies can be detected also in patients with SSc, but they are generally less commonly present than in adults with rheumatoid arthritis [95]. In a few studies, significant association has been detected between anti-CCP positivity and the presence of arthritis and marginal erosions. Thus, it has been suggested that high titers of anti-CCP antibodies may help to define the diagnosis of SSc–RA overlap syndrome [75,96–98]. In contrast, Avouac et al., found no significant difference between patients with and without arthritis or erosions in terms of presence of anti-CCP2 antibodies [88]. Generini et al. did not find significant association between anti-CCP positivity and articular involvement either, though it must be noted, that they had a small number of anti-CCP positive patients ($n$ = 3) [99]. Ueda-Hayakawa et al. suggested the combined use of anti-CCP, RF and anti-agalactosyl IgG antibodies, because 91% of their SSc–RA overlap patients were positive for two or more of these RA-related antibodies [100]. In conclusion, RF and anti-CCP antibodies might be more common in SSc–RA overlap patients than in SSc patients without RA; however, the presence of RF of anti-CCP by itself does not give sufficient help in the establishment of RA diagnosis in SSc patients, though their combined presence with anti-agalactosyl IgG antibodies might give further help.

## Evaluation and examination

The assessment of arthritis is very difficult in SSc due to certain characteristics of the disease: skin oedema, thickening and tethering, digital ulcers, subcutaneous calcinosis and contractures [84]. It has also been pointed out that physical examination is not sensitive enough to assess arthritis in SSc [84,101,102]. So far, there is no fully validated and universally accepted assessment technique for assessing arthritis in SSc by physical examination. The 8 joint count has been used in a few studies [24,53,82,83,85,103]. This assesses swelling and tenderness of the MCPs (as a whole on each hand), the wrists, elbows, and knees as absent or present. The 28 joint swelling and tenderness count – as part of the DAS28 disease activity index – is a worldwide accepted tool for assessing arthritis in RA [104,105]. This particular instrument has also been used in SSc in two studies [56,103], although its validity has not been proved in scleroderma. Its adaptation to SSc may be considered because the joint involvement pattern of SSc may differ from that of RA. Unlike RA, the DIP joints are often involved in SSc, as erosions and joint space narrowing are frequently seen on hand X-ray. However, the presence of concomitant osteoarthritis cannot be excluded, either [58,88,90]. Besides DAS28, the adaptation of other articular indices – used in RA – may be considered for joint assessment in SSc, e.g. the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI).

The association of acute phase reactant elevation – indicating systemic inflammation – and the arthritis detected by physical evaluation, radiography, MRI, US and Doppler US have been reported by a number of studies [30,40,84,88,90,94]. Moreover, in the study of the EUSTAR cohort of more than 6000 patients, clinical synovitis had the highest strength of association with elevated acute phase reactants taken as the dependent variable. This was true in both the lSSc and dSSc subsets, and in all disease stages [30]. The radiographic signs of joint inflammation are also associated with an increased CRP [90]. However, it must be noted, that CRP elevation is a marker of current inflammation, while marginal erosions, juxta-articular osteoporosis and joint space narrowing are signs of long term

inflammation that is not necessarily present at the moment [62].

Articular involvement was assessed also by imaging in a number of studies. Radiographic studies are the most common, but there are also a few studies about ultrasound imaging, magnetic resonance imaging, thermography and bone scan [58–63,75,86,88,90,93,94,101,102,106–111]. The most frequent articular findings by imaging were joint space narrowing (JSN), erosions, and contractures.

In the study of Blocka et al., all radiographic findings showed progression, although isolated reversibility was also noted [59]. In the longitudinal study of Avouac et al., radiographic progression of erosive arthritis was seen in 24%, acroosteolysis in 22% and flexion contracture in 18% of the patients over a median of 5-year follow-up period [107].

Though joint space narrowing can be a sign of previous synovitis, it can also be the consequence of osteoarthritis. JSN in SSc is most frequently seen in the DIPs, but it is also common in the other joints of the hand. It is not clear whether the high frequency of JSN in the DIPs in SSc patients is part of the articular manifestations of scleroderma or if it is caused by concomitant osteoarthritis of the hands [58,90]. In the US study of Cuomo et al., SSc patients displayed significantly lower prevalence of JSN than patients with RA [94]. In terms of SSc cutaneous subsets, Erre et al. found no significant differences in the prevalence of JSN [90].

Erosions in SSc are often similar to those seen in rheumatoid arthritis, however, they are less frequent [63,94]. However, in SSc well-circumscribed foci of osseous resorption or erosions on the dorsal aspects of metacarpal or proximal phalangeal heads can be also found [59]. Erosions are most frequently detected in PIP and MCP joints; however erosions can be present in the DIPs, too [58,84,88,90]. Avouac et al. reported that 72% of the patients with erosions had erosive changes in the DIP joints. Of note is that most of their patients were post-menopausal women, thus, the possibility of an arthropathy, unrelated to SSc could not be ruled out [88]. In contrast to this, Blocka et al. found no erosions in the distal interphalangeal joints in their study [59].

Cuomo et al. reported that the prevalence of joint effusions did not differ between SSc and RA patients, but SSc patients displayed a significantly lower prevalence of synovial proliferation and power Doppler signal. They found joint effusions and synovial proliferation in 22%; while synovial proliferation altogether in 42% of 45 consecutive SSc patients [94]. Elhai et al. detected inflammatory synovitis by US in more than half of the 52 consecutive SSc patients. Synovitis by US was found in the wrists and hand joints of SSc patients without a statistically significant difference when compared to the RA patients. They have also reported that SSc patients with disease duration of 3 years or less had significantly more clinical synovitis than those whose disease duration was more than 3 years; however, the prevalence of US synovitis was not significantly different between the early and the late disease stage groups [84].

Flexion contractures emerge as the most frequent articular abnormality on radiographs in SSc, they are present in nearly 90% of all patients [59]. The prevalence of finger flexion contractures is significantly higher in patients with dSSc compared with lSSc [61,88].

Calcium deposits most often occur in the subcutaneous soft tissues; however, they may also develop in the tendons, peritendinous or periarticular areas [108]. In the study of Cuomo et al., osteophytosis was detected in 58%, and periarticular calcinosis in 27% of SSc patients by US. They found no difference in the prevalence of osteophytes in SSc and RA patients [94]. Erre et al. – in agreement with Avouac et al. – reported association between calcinosis and erosions; nevertheless, they were not able to demonstrate a complete topographic overlapping of these lesions. Thus, the pathogenic role of calcinotic deposits on the occurrence of erosive arthritis is not completely sustained by these results [88,90].

Similarly to erosions and joint space narrowing, juxta-articular osteoporosis and osteopenia are periarticular signs of long term joint inflammation. The prevalence of juxta-articular osteoporosis detected by radiography is between 4 and 42% [58,59,61,75,90,112]. No significant difference was detected in the frequency of juxta-articular osteoporosis between lSSc and dSSc [90]. Though clinical sign of arthritis is more common in dSSc than in lSSc, the similar prevalence of juxta-articular osteoporosis in the two subsets indicate that subclinical inflammation of the joints is as frequent in lSSc, as in dSSc.

The resorption of the distal phalanges, also called as acroosteolysis, is quite common is SSc with a frequency of 9 to 63%. Although it is mostly progressive, there is evidence of improvement in a few cases [63]. It is not clear whether its frequency differs among the limited and diffuse cutaneous forms of the disease or not [75,77,90,110]. It is usually studied by radiography; however, Freire et al. recently reported that sensitivity of US was similar to radiography in acroosteolysis detection. In their study, the majority of patients with tuft resorption also exhibited power Doppler US signal adjacent to the acroosteolysis bed, in some cases, even when distal vascularization was not detected. They suggested this might be secondary to granulation tissue to induce bone formation in an attempt to repair the osteolysis [108].

While resorption of distal phalanges is the most common, osteolysis in other sites including feet, ribs, and mandibles may also occur. In the study of Bassett et al., 7 of the 55 patients exhibited partial destruction of ribs 2–6, and 6 of the 35 patients presented with osseous resorption around the mandibular angles [63]. Resorption of the distal ulna was reported in 2% of the patients in four studies, while previously it was found in 8% of the patients in the study of Baron et al. [58,60,84,88].

### Prognosis

The presence of arthritis was also found to be associated with markers of severe vascular (elevated SPAP > 40 mmHg) and muscular (muscle weakness) involvement and with increased Health Assessment Questionnaire (HAQ) disability score [30,88]. In contrast, US detected synovitis did not correlate with HAQ-DI [94]. This disagreement can be explained by the fact that US might detect not only painful and disabling synovitis, but also subclinical synovial effusions as well.

The resorption of distal phalanges is significantly associated with digital ulcers and extra-articular calcification, interstitial lung disease, reduced forced vital capacity (FVC), esophagus involvement, and more severe disease [88,90,109].

SSc patients with joint contractures are more likely to experience severe vascular and muscular disease, as well as to have elevated acute phase reactants [30]. Flexion contractures detected by radiography are reported to be associated with interstitial lung disease, reduced FVC, esophagus involvement and high HAQ disability score [88,90].

According to a study of Avouac et al., the presence of digital ulcers independently predict progression of acroosteolysis [107]. In multiple logistic regression analysis, calcinosis and PAH were associated with acroosteolysis as dependent variable [88].

### Treatment

There have been very few studies assessing the therapy of synovitis in SSc. In analogy to rheumatoid arthritis, SSc patients with arthritis are usually treated with DMARDs and corticosteroids. Only limited information is available concerning the efficacy of methotrexate, azathioprine, and mycophenolate mofetil. Su et al. have found that methotrexate did not decrease significantly the mean of tender joint count and number of areas affected by tendon friction rubs over the 48-week study. They have observed similar results with rapamycin, an IL-2 inhibitor [85].

According to the EULAR recommendations consistent with expert opinion, low dose of steroids is commonly used for the treatment of inflammatory arthritis in patients with SSc, however, its efficacy has not been proved in any randomized controlled trial [113]. Corticosteroids should only be given in low dose ($\leq$ 10 mg) and with great precaution due to the risk of inducing renal crisis [114].

A pilot study conducted by Nacci et al. suggested that intravenous immunoglobulins (IVIG) might reduce joint pain and tenderness, with a significant recovery of joint function in patients with SSc with severe and refractory joint involvement [103]. However, the high cost of IVIG will probably not allow its extensive use among SSc patients with arthritis. D-Penicillamine has been found to be ineffective in the treatment of SSc arthritis in a two-year, double-blind, randomized, controlled clinical trial [24].

Cyclophosphamide was reported by two randomized, controlled clinical trials to be effective in the treatment of SSc-related interstitial lung disease [115,116]. However, there were no differences in musculoskeletal measures (joint swelling, joint tenderness, large joint contractures, muscle tenderness, muscle weakness, fist closure) between the cyclophosphamide and placebo groups at baseline, 12 and 24 months in the Scleroderma Lung Study [53].

In a pilot study of a small group of patients, tocilizumab and abatacept appeared to be safe and effective on joints, in patients with refractory SSc [56].

Recombinant relaxin was also tested in the treatment of SSc articular involvement, however, it turned out to be of no help in reducing functional disability in patients with dSSc, moreover, it was associated with serious renal adverse events [83].

Tumor necrosis factor alpha inhibitors appeared to be efficient in the treatment of SSc joint involvement in two small studies [117,118], but did not show clear benefit in a third study [119]. However, according to the consensus of the EUSTAR experts, their use should be limited to clinical trials due to the potential danger of severe exacerbation of pulmonary fibrosis [120].

In cases of marked damage, hand function may be significantly improved by surgery in some patient. Pain reduction can also be a surgical goal in some cases [121].

There are no drugs available so far that have been proven to improve calcinosis [113].

### Conclusion

Skeletal involvement is frequent in SSc. Patients with SSc have an increased risk for developing osteoporosis, thus patients should be regularly screened. Patients with early disease, diffuse subset, joint complaints or elevated acute phase reactants should be evaluated for arthritis and contractures. Since joint involvement can be the initial manifestation of the disease, SSc should be considered in the differential diagnosis of patients with arthritis, especially in those with other SSc-related features e.g. puffy fingers, ANA positivity, nail fold capillaroscopy changes. Contractures start to develop in the very early stage of the disease, thus range of motion should be assessed regularly from the first visit of the patients. Patients with joint contractures should be monitored closely for development or deterioration of vascular or muscle involvement.

In case of articular complaints, symptoms or signs, imaging and laboratory examinations (X-ray, US, acute phase reactants) are also needed. Arthropathy in SSc appears to be progressive in most of the cases. We are still lacking evidence-based therapeutic and preventive strategies for musculoskeletal involvement of SSc. Besides low doses of corticosteroids, methotrexate, leflunomide, azathioprine, mycophenolate mofetil are given as off-label drugs in SSc, as we are lacking large, controlled studies assessing these drugs in the treatment of SSc-related arthritis.

## Tendon involvement

Tendon friction rubs and tenosynovitis are the major kind of tendon involvement described in SSc. Tendon friction rubs

(TFRs) are characterized by a leathery crepitus felt above the tendons [122]. This does not necessarily mean the inflammation of the tendon sheath.

### Prevalence

According to the EUSTAR database, the prevalence of TFRs in SSc is about 11%. It can be found in both subsets and in all disease stages; however it is more common in patients with dSSc, early disease and in the Caucasian race [30,77,82,123]. In the study of Elhai et al., tendon friction rubs were only found in those patients, who also had tenosynovitis detected by US [84].

Only few data are available concerning the frequency of true tenosynovitis in SSc. By clinical assessment, tenosynovitis was diagnosed in 16% of 38 consecutive SSc patients and in 12% of SSc patients with a history of hand or wrist joint pain and/or swelling [101,106]. The frequency of tenosynovitis detected by US or MRI is approximately 27% among consecutive SSc patients [84,108]. Stoenoiu et al. reported similar frequency in consecutive dSSc patients [124]. Tenosynovitis by MRI was found in 47–88% of SSc patients with a history of articular involvement [40,101,102]. A study among consecutive SSc patients has also been conducted, where tenosynovitis was found in 11% of the patients by MRI [106].

### Clinical symptoms

Some patients are not only aware of the friction rubs, but also complain about accompanying pain [123]. Pain along the tendon, that is not restricted to the nearby joints, can also be a sign of true tenosynovitis.

### Evaluation and examination

TFRs can be rapidly assessed during routine physical examination by an experienced examiner. According to Steen et al., the best way of evaluating the presence of TFR is by placing ones digits with palmar aspect across the examined tendon, and asking the patient to move the underlying joint through the possible range of motion. In case tendon friction rubs are present, a leathery, rubbing, ''squeaking'' sensation will be noted by the examiner and sometimes by the patient, too. Rubs may be present in numerous areas, however the following tendons are most frequently involved: extensor and flexor tendons of the fingers and wrists, and tendons over the elbow (triceps), knees (patellar), and ankle (anterior and posterior tibial, peroneal, and Achilles). Shoulder, scapular, trochanteric or toe rubs can also be noted, but less commonly. Most often TFR are easily reproducible, however they might be intermittent or disappear with repeated movements. Usually patients have rubs in more than one body region, thus the presence of TFR can be unequivocally determined [123].

When pain and tenderness on palpation of a certain tendon raises the suspicion of tenosynovitis, the diagnosis can be confirmed by US examination. Elhai et al. detected a power Doppler signal corresponding to an inflammatory activity in 54% of tendons with tenosynovitis, and hyperechoic tendon sheath thickening, a pattern considered as sclerosing in 43% of the tendons with US tenosynovitis. This pattern appeared to be specific to SSc patients as compared to RA [84].

### Prognosis

Steen et al. have pointed out the predictive value of TFRs in establishing the diagnosis of dSSc in an early stage [123]. This was confirmed in the study of Ostojic et al. [77]. Khanna et al. have assessed the significance of TFRs in early dSSc in a randomized controlled trial and found that the presence of TFRs was associated with a higher HAQ-DI. They have also observed that changes in TFR predicted changes in MRSS and HAQ-DI, thus the appearance of TFRs was associated with active disease [82]. Moreover, patients with TFRs have a more than 2-fold risk of developing renal crisis and cardiac and gastrointestinal disease complications compared to patients without this finding. Patients with TFRs also have reduced survival rates [125]. In the EUSTAR cohort, significant associations have been found between the presence of TFRs and digital ulcers, muscle weakness, pulmonary fibrosis on plain chest X-ray, and proteinuria. The presence of TFRs may indicate the existence of a severe vascular, interstitial lung, and renal involvement, regardless of the disease stage [30].

Elhai et al. evaluated the correlations of tenosynovitis detected by US. They found that US tenosynovitis was associated with joint space narrowing in the wrist, radiologic demineralization, higher modified Rodnan skin score, presence of anti-Scl-70 antibodies, more active and severe disease. US tenosynovitis was more likely to occur in patients with tendon friction rubs, in those with a higher finger to palm distance, and in those with higher number of painful and swollen joints. Moreover, the presence of anti-Scl-70 antibodies and radiologic demineralization were independently associated with tenosynovitis in multivariate analysis [84].

### Conclusion

It is very important to search for TFRs, particularly in the first years of SSc, however appropriate assessment requires some experience. Tendon friction rubs can be regarded as a marker of severity of SSc and patients presenting with TFRs should be carefully monitored for serious internal organ involvement. Tenosynovitis characterized by true inflammation of the tendon, pain and sometimes swelling can also be present in SSc. In case suspicion is raised by clinical evaluation, further examination by US might be needed.

## Disability and quality of life

Johnson et al. found that joint involvement in SSc is more disabling than joint involvement in psoriatic arthritis; and patients with SSc experience more severe pain than patients with RA. Physical health relating to quality of life is adversely affected in patients

with SSc and disability is associated with the joint involvement [126]. Skin and musculoskeletal involvement in SSc is usually most prominent on the hands, thus hand function can be dramatically reduced. In the Canadian National Survey among more than 400 SSc patients, complaints related to decreased hand function were frequently endorsed (67% of the patients), and were commonly associated with remarkable impact on daily activities [57]. In the diffuse subset of SSc patients, the development of functional impairment is quite rapid: significant functional impairment is present in about half of the patients within the first 18 months after onset of the disease [87].

Health related quality of life (HRQOL) perceived by SSc patients is significantly impaired compared with healthy individuals. Moreover, Hyphantis et al. found that SSc patients have impaired HRQOL in comparison with RA, SLE, and Sjögren patients, when age, pain, psychopathology, and coping strategies were taken into account [89].

Many different tests and questionnaires have been developed in order to measure hand function, quality of life and global disability in rheumatic patients. Some of these have been primarily developed for SSc, others have been adapted to SSc or validated for SSc without any changes from another disease. Clements et al. recently evaluated the validity of various potential outcome variables for the assessment of articular involvement according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter [127]. Thus, we will only briefly introduce the Health Assessment Questionnaire; which is undoubtedly the most important instrument in measuring disability in SSc. It is a patient questionnaire that has been fully validated in SSc and translated into many languages [128,129]. In the high-dose versus low-dose D-penicillamine study, it has also been shown that HAQ is a predictor and correlate of outcome in SSc [87]. Rannou et al. showed that hand disability was the far most important determinative of disability measured by HAQ in SSc [79].

## Disease activity

The European Scleroderma Study Group (EScSG) developed preliminary disease activity indices to be used in SSc patients [130,131]. However, these criteria await further validation, as further work is requested to prove their responsiveness. In this particular index, musculoskeletal involvement is represented by the presence of bilateral arthritis.

Based on clinical observations, additional clinical parameters that could indicate the activation of musculoskeletal system might be the worsening in the musculoskeletal symptoms, active myositis, symptoms corresponding to carpal tunnel syndrome and the presence of tendon friction rubs [30,82,125]. Definition criteria and consensus assessment methods of these types of involvements are still lacking, therefore it is difficult to define their precise role in the assessment of disease activity.

Attempts were made to improve the EScSG activity index [132]. Regarding the musculoskeletal component of the disease, the value of HAQ-DI, and the change in HAQ-DI was incorporated into the so-called 12-point activity index. The number of contractures was also found to be correlated to both the EScSG activity index and the 12-point activity index. CRP has shown the same association with these two indices [132]. Of note is that in the study of the EULAR cohort of more than 6000 patients, clinical synovitis had the highest strength of association with elevated acute phase reactants taken as the dependent variable. This was true in both lSSc and dSSc subsets [30]. The radiographic signs of inflammation (occurrence of marginal erosions with the exception of DIP joint erosion and/or juxta-articular osteoporosis in association to space narrowing of proximal interphalangeal joints) were also associated with an increased CRP in another study [90]. CRP also correlated with the HAQ-DI [133]. Therefore, the elevation of CRP might reflect an underlying musculoskeletal activity in SSc.

## Musculoskeletal rehabilitation

There have been a few small studies investigating different musculoskeletal rehabilitation techniques in SSc. The main techniques that have been proved to have beneficial effect on hands are hand range of motion exercises, paraffin wax bath, connective tissue massage, manual lymph drainage and patient education [134–140]. Splinting was also studied, however did not turn out to be useful [141]. Recently studies are not only focused on the rehabilitation of the hands, but also on orofacial rehabilitation and overall rehabilitation programs – consisting of specific and global techniques [134–140].

Mouth opening, functional ability, hand function and mobility can be improved by overall rehabilitation. The advantages of overall rehabilitation in SSc have been studied in two recent studies with similar results. However, with a few exceptions – e.g. hand mobility, grip strength – these results tend to disappear over a relatively short period, within a few months after the end of the rehabilitation programs. Thus, these programs should be either continuous or regularly repeated in order to sustain their benefits [142,143].

## Conclusion

The overall summary is that musculoskeletal involvement:

- is very frequent in SSc;
- is often among the initial manifestations of the disease;
- causes significant disability hence decreases quality of life;
- if present, may predict more severe internal organ involvement.

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