

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

Ph.D. thesis

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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
DAI	disease activity index
DAS28-CRP	Disease Activity Score of 28 Joints using C-reactive protein
DAS28-ESR	Disease Activity Score of 28 Joints using erythrocyte sedimentation rate
dcSSc	diffuse cutaneous systemic sclerosis
DIP	distal interphalangeal joint
DLCO	diffusion capacity of the lung for carbon monoxide
EScSG-AI	European Scleroderma Study Group Activity Index
ESR	erythrocyte sedimentation rate
FTP	Finger to Palm Distance
HAI	Hand Anatomic Index
HAQ-DI	Health Assessment Questionnaire Disability Index
lcSSc	limited cutaneous systemic sclerosis
MCP	metacarpophalangeal joint
MRI	magnetic resonance imaging
MSAI	Modified Scleroderma Activity Index
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PIP	proximal interphalangeal joint
qDASH	Quick Questionnaire of the Disability of the Hands, Arms and Shoulders
RA	rheumatoid arthritis
RP	primary Raynaud's phenomenon
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
VAS	visual analogue scale

## **1. BACKGROUND**

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.

The severity of a systemic connective tissue disease is determined by disease activity, the potentially reversible phenomena of the disease and by the resulting 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 hand. 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.

Tools and drugs used in the management of rheumatoid arthritis (RA) might also be useful regarding SSc, because there are many resemblances in the articular involvement of these two diseases. In the management of RA, “treat to target” attitude 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) and the Disease Activity Score of 28 joints using CRP (DAS28-CRP). Later the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI) were created to allow calculation of disease activity without a computer.

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.

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. AIMS**

### **2.1. 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 patient cohort. The question of extending the 28 joint count by the distal interphalangeal (DIP) joints in SSc was also addressed.

## **2.2. 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.

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

Joint contractures develop early in the course of SSc due to underlying 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. 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 (Outcome Measures in Rheumatoid Arthritis Clinical Trials) filter in SSc.

# **3. PATIENTS AND METHODS**

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

This study 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.

(1) Seventy-seven patients with SSc were included from the Department of Rheumatology and Immunology, University of Pécs. Patients unable to cooperate, patients with end stage internal organ involvement, significant joint pain or disability not caused by SSc were excluded. Cohort enrichment was performed to increase the proportion of patients with early disease and diffuse cutaneous systemic sclerosis (dcSSc). Recruitment of patients with long standing disease was stopped after reaching a predefined number (n=55), while enrolment of patients with early disease continued throughout the recruitment period. Forty consecutive patients with RA were included in the control group.

(2) The DeSSciphier project is a multinational study embedded in the European Scleroderma Trials and Research (EUSTAR) group database. SSc patients with at least 2 swollen and tender joints on physical examination were enrolled into the “Arthritis group” (n=100). SSc patients with less than 2 tender and swollen joints 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 study. Patients were recruited at 34 study sites from 14 countries.

Data of patient groups were compared by Fisher’s exact test, Mann-Whitney U test and independent sample T test depending on the type of each variable. Comparison of left and right side was done by McNemar test.

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

Forty patients with SSc (18 lcSSc / 22 dcSSc), 34 patients with RA and 21 healthy individuals took part in this study at the Department of Rheumatology and Immunology, University of Pécs. Patients were evaluated by the DAS28-ESR, the Finger to Palm distance (FTP) and the Hand Anatomic Index (HAI). In addition to the CHFS all participants filled out the Health Assessment Questionnaire Disability Index (HAQ-DI) and the adjacent visual analogue scale measuring pain (Pain-VAS).

We translated and adapted CHFS to Hungarian culture using the “forward-backward translation method” and validated it according to the OMERACT filter.

### **3.3. Validation of articular DAIs in SSc**

In addition to the 77 patients with SSc and 40 patients with RA described in details previously (see section 3.1) 20 patients with primary Raynaud’s phenomenon (RP) and 28 healthy volunteers were recruited as control groups.

Articular disease activity was assessed using DAS28-ESR, DAS28-CRP, CDAI and SDAI. Disease activity of SSc was evaluated by the European Scleroderma Study Group Activity Index (EScSG-AI) and the Modified Scleroderma Activity Index (MSAI). Structural damage was examined by the HAI and the Delta Finger to Palm Distance (delta-FTP) and the 28 joint contracture count (CoC28). All participants filled out the HAQ-DI, the CHFS, Quick Questionnaire of the Disability of the Hands, Arms and Shoulders (qDASH), the Scleroderma Health Assessment Questionnaire (SHAQ) and the 36-Item Short Form Health Survey (SF36). The OMERACT filter was used to assess the validity of the DAIs.

The subjects' written informed consent and ethical authorisation was obtained for all three studies.

## 4. RESULTS

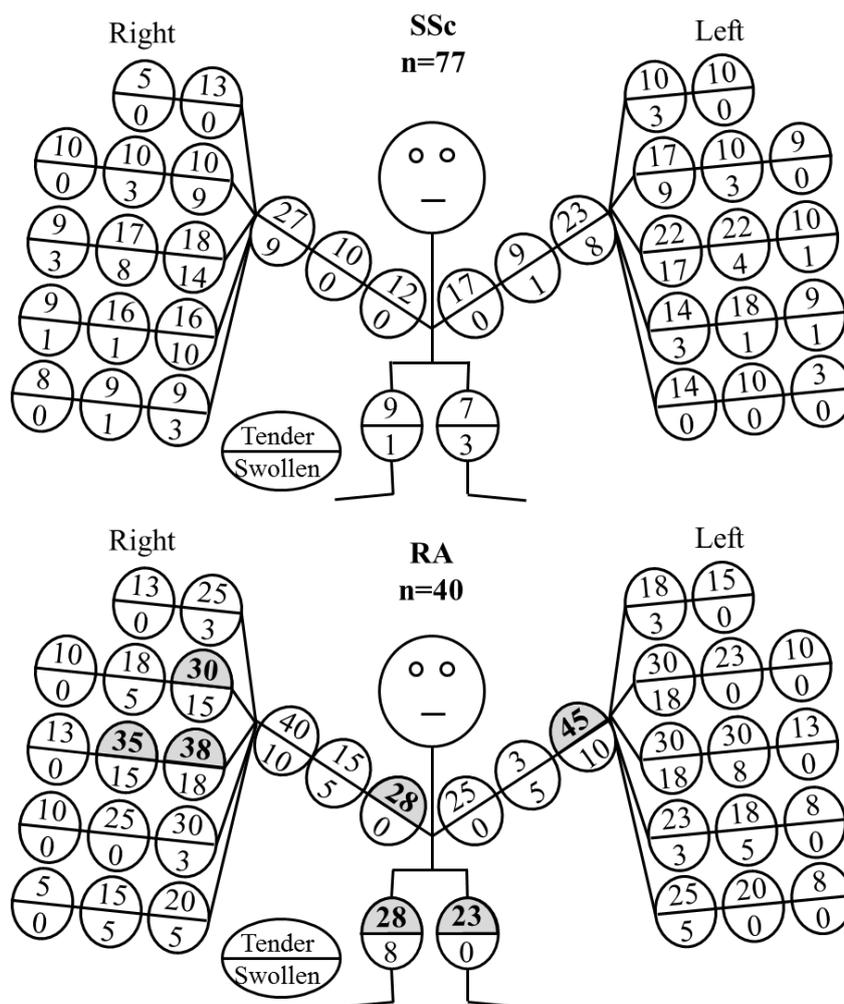
### 4.1. Investigation of distribution of joint involvement in SSc

#### 4.1.1. Single centre study

In the RA cohort (36 females/4 males, age: 59.3±8.1 years, disease duration: 15.2±9.1 years) 26 patients were rheumatoid factor positive, and 24 were anti-cyclic citrullinated peptide (anti-CCP) positive, while in the SSc cohort (67 females/10 males, age 56.3±11.8, years, disease duration: 10.5±9.5 years) 18 patients were rheumatoid factor positive and one patient was anti-CCP positive.

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).

**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*

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 metacarpophalangeal (MCP) and the proximal interphalangeal joints (PIP) 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 and the RA cohort. The prevalence of swelling was significantly higher in the right IV. MCP joint, than 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.

#### **4.1.2. Multicentre study**

Patients with arthritis had a higher rate of female gender (94% vs. 84%;  $p = 0.006$ ), higher frequency of muscle involvement (29% vs. 19%  $p = 0.025$ ) and higher prevalence of decreased DLCO under 70% (75% vs. 60%,  $p = 0.015$ ) compared to “Non-arthritis group”. All further analyses were done using data of the “Arthritis group”.

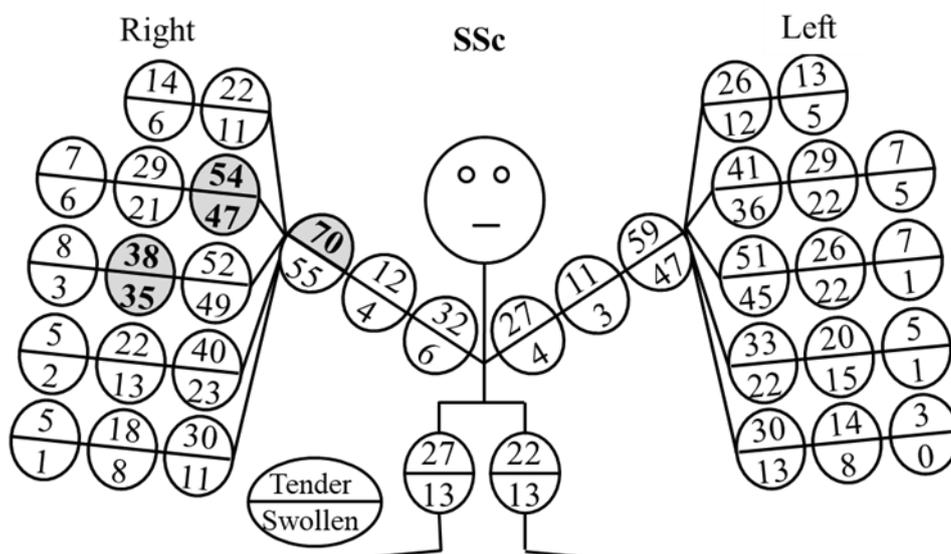
Distribution of joint tenderness was similar to distribution of swelling in the examined SSc patients. The wrists, the second, and the third MCP joints were most often tender and most often swollen. (Figure 2)

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 joint involvement in the early (i.e. disease duration  $< 3$  years) and late cases (i.e. disease duration  $\geq 3$  years).

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 (67 %

vs. 60 %,  $p=0,039$ ) and swelling of the second MCP joint (54% vs. 39%,  $p=0.008$ ) was significantly more frequent on the right side of patients with lcSSc, than on their left side.

**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.*

#### 4.2. 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.

##### 4.2.1. Construct validity

Spearman's rank-correlation analysis showed strong correlation between CHFS and HAQ-DI in patients with SSc ( $\rho=0.709$ ,  $p<0.001$ ) and RA ( $\rho=0.831$ ,  $p<0.001$ ). CHFS also showed significant correlation with tests referring to structural hand damage such as HAI ( $\rho=-0.512$ ,  $p<0.01$ ) and Delta-FTP ( $\rho=-0.649$ ,  $p<0.001$ ) in patients with SSc. Significant correlation was found between CHFS and DAS28-ESR in patients with SSc ( $\rho=0.454$ ,  $p<0.01$ ) and RA ( $\rho=0.471$ ,  $p<0.01$ ). However, there was not any correlation between CHFS and CRP, as well as CHFS and ESR. Pain-VAS and CHFS showed significant correlation in the SSc ( $\rho=0.624$ ,  $p<0.001$ ) and the RA group ( $\rho=0.365$ ,  $p<0.05$ ).

##### 4.2.2. 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.

#### **4.2.3. Structural validity**

The questions were combined into two main components by the principal component analysis. The first dimension comprises 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 contains questions concerning dexterity and fine motoric skills (question 5.,6.,8.,13.,14.,16. and 17.).

#### **4.2.4. Discriminative validity**

There was a significant difference regarding the CHFS and pain-VAS values of the SSc and the control group ( $p < 0.05$ ), and also between the values of the RA and the 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. We found statistically significant difference between the CHFS scores of SSc patients with severe hand damage and SSc patients with mild hand damage ( $HAI \leq 2$  vs.  $HAI > 2$ ;  $\Delta\text{-FTP} < 7\text{cm}$  vs.  $\Delta\text{-FTP} > 7\text{cm}$ ) by Mann-Whitney U test ( $p < 0.05$ ). However, there was no significant difference in hand function measured by CHFS between patients with lcSSc and with dcSSc. There was significant difference regarding CHFS scores between RA patients with severe structural hand damage ( $HAI \leq 2$ ,  $n=15$ ) and RA patients with mild structural hand damage ( $HAI > 2$ ,  $n=19$ ) ( $p < 0.01$ ).

#### **4.2.5. Reliability: internal consistency and reproducibility**

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

### **4.3. Validation of articular DAIs in SSc**

#### **4.3.1. Construct validity**

DAS28-ESR, DAS28-CRP, and SDAI showed significant correlation with disease activity measured by the EScSG-AI and the MSAI. High correlation was observed between articular disease activity assessed by the physician on VAS and DAS28-ESR as well as DAS28-CRP. The articular DAIs showed strong correlation with measures of disability (HAQ, CHFS, qDASH, VAS of overall scleroderma symptoms). SF36 Physical Component Summary (PCS) showed significant correlation with all four articular DAIs, while SF36 Mental Component Summary (MCS) showed only weak

correlation with SDAI and CDAI, and no correlation with DAS28-ESR and DAS28-CRP (Table 1). There was no correlation between the articular indices and the following parameters: age, disease duration, Modified Rodnan Skin Score (MRSS), HAI, Delta-FTP, CoC28.

**Table 1 Spearman’s correlation analysis of disease activity indices with functional status and disease activity measures in 77 patients with systemic sclerosis (SSc)**

SSc n=77	DAS28 -ESR <sup>a</sup>	DAS28 -CRP <sup>b</sup>	SDAI <sup>c</sup>	CDAI <sup>d</sup>
MSAI <sup>e</sup>	.402***	.356**	.366**	.363**
EScSG-AI <sup>f</sup>	.344**	.337**	.355**	.345**
VAS-physician <sup>g</sup>	.701***	.749***	-	-
HAQ-DI <sup>h</sup>	.495***	.485***	.477***	.486***
CHFS <sup>i</sup>	.422***	.350**	.344**	.356**
QDASH <sup>j</sup>	.617***	.595***	.589***	.599***
VAS-overall (sHAQ <sup>k</sup> )	.469***	.458***	.492***	.503***
VAS-Raynaud (sHAQ)	.330**	.336**	.354**	.365**
VAS-pain (HAQ)	.515***	.526***	.548***	.562***
VAS-joint pain	.640***	.680***	.711***	.716***
VAS-fatigue	.476***	.456***	.488***	.502***
SF36 PCS <sup>l</sup>	-.578***	-.565***	-.568***	-.583***
SF36 MCS	-.192	-.193	-.255*	-.243*

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , Abbreviations: <sup>a</sup>Disease Activity Score of 28 Joints using erythrocyte sedimentation rate, <sup>b</sup>Disease Activity Score of 28 Joints using C-reactive protein, <sup>c</sup>Simplified Disease Activity Index, <sup>d</sup>Clinical Disease Activity Index, <sup>e</sup>Modified Scleroderma Activity Index, <sup>f</sup>European Scleroderma Study Group Activity Index, <sup>g</sup>physician’s assessment of disease activity on a visual analogue scale; <sup>h</sup>Health Assessment Questionnaire Disability Index, <sup>i</sup>Cochin Hand Function Scale, <sup>j</sup>Quick Questionnaire of the Disability of the Hands, Arms and Shoulders, <sup>k</sup>Scleroderma Health Assessment Questionnaire, <sup>l</sup>36-Item Short Form Health Survey Physical Component Summary and Mental Component Summary

#### 4.3.2. Content validity

Regarding 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 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,

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.

#### **4.3.3. Structural validity**

Principal component analysis was performed to check for the unidimensionality of the articular DAIs. The components of the indices 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.

#### **4.3.3. Discriminant validity**

Significant differences were seen in these particular composite indices comparing patients with SSc and patients with RA ( $p=0.002$ ), patients with primary Raynaud's phenomenon ( $p=0.001$ ) and healthy controls ( $p=0.000$ ).

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 ( $n=66$ ) ( $p<0.05$ ). There was not any significant difference regarding DAS28-CRP in these particular subgroups ( $p=0.064$ ). Significant difference was found in the values of DAS28-ESR of SSc patients with  $ESR \leq 30$  mm/h and patients with  $ESR > 30$  mm/h ( $p=0.014$ ). There was also significant difference regarding SDAI as well as DAS28-CRP values of SSc patients with  $CRP \leq 5$  mg/l and patients with  $CRP > 5$  mg/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  $HAQ-DI \geq 1$  ( $p<0.001$ ). Subgroups of RA based on HAQ-DI values ( $<1$  vs.  $\geq 1$ ) 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 ( $\leq 4$  years vs.  $>4$  years), MRSS ( $\leq 14$  vs.  $>14$ ) and HAI ( $\leq 2$  vs.  $>2$ ), presence or absence of digital ulcers, ulcers on the extensor surface of the joints, and subcutaneous calcinosis ( $p>0.05$ ).

#### **4.3.4. Reliability and feasibility**

Intraclass correlation coefficient for the assessment of interobserver reliability of DAS28-ESR, DAS28-CRP, SDAI and CDAI was 0.89, 0.89, 0.71, 0.70, respectively ( $p<0.001$ ). Intraclass correlation coefficient evaluating intraobserver reliability of DAS28-ESR, DAS28-CRP, SDAI and CDAI was 0.98, 0.97, 0.92, 0.92, respectively ( $p<0.001$ ). Each assessment lasted 3 to 5 minutes.

## 5. DISCUSSION

### 5.1. 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. The higher prevalence of symptoms in regarding most of the joints in the multicentre cohort compared to the single centre 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 is in concordance with findings in RA. 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. 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 patient 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. This might be explained by two factors. (1) Joint tenderness and swelling are reversible abnormalities, that can subside spontaneously or due to drugs (e.g. 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 the radiologic 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. 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.

Synovitis, muscle weakness and decreased DLCO are all known unfavourable prognostic factors in SSc. This might explain the differences found between the “Arthritis group” and the “Non-arthritis group” in the DeSSciper 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.

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

In accordance with previous studies CHFS showed the strongest correlation with HAQ-DI in patients with SSc ( $\rho=0.709$ ) and RA ( $\rho=0.831$ ). This indicates a strong association between the functional state of the hands, the patients’ general functional state and their self-efficacy. CHFS indicated the condition of the hands in both disease groups in consonance with the HAI, which demonstrates anatomic hand damage. There was only partial correspondence between CHFS and disease activity, because it showed positive correlation with the DAS28-ESR, but it did not show significant correlation with ESR, or with CRP.

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; while we did not find any further data regarding this aspect of the test in other studies.

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. Most of the previous studies found significant difference between the hand function of patients with dcSSc and lcSSc. 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 were remarkably higher in the lcSSc group – that usually has better hand function – than in the dcSSc group. Altogether, 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 high Cronbach’s alpha and intraclass correlation coefficient – similar to that seen in the French study – show that overall reliability of the test did not change during its cross-cultural

adaptation to Hungarian. Feasibility of CHFS was proven, since its cost, equipment, time requirements were minimal.

The limitations of this study were the relatively small number of patients and its cross-sectional nature. 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.

### **5.3. 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. 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. 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.

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, Delta-FTP and CoC28. Moreover, disease duration and age did not show any correlation with the articular DAIs either, which also supports 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 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 severe 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 the changes seen in patients with RA.

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, 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 high correlation of the articular indices with HAQ-DI QDASH and CHFS can be explained by the fact, that the majority of the joints assessed in the 28 joint counts refer to the upper limb.

Floor and ceiling effects were not present at either of the articular DAIs, however, 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. This does not decrease the value of the DAIs in SSc patients with inflammatory joint complaints.

Discriminant validity was proven for all four articular DAIs. 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 the EScSG-AI.

Regarding reliability, the DAS28-ESR performed best among the four indices, however good interobserver and intraobserver reliability was proved for all articular indices. Additional training is not required for rheumatologists experienced in the assessment of patients with RA.

Feasibility was proven for all four articular indices. 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.

In this study DAS28-ESR showed the best results regarding construct validity, discrimination and reliability. 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 with SSc did not have 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. 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. 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. 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.

## **6. NEW RESULTS**

6.1.1. 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.

6.1.2. 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.

6.1.3. 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.

6.1.4. 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.

6.1.5. 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.

6.2.1. 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.

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

6.3.1. 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.

6.3.2. 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.

6.3.3. 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).

## **7. 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” in the management of SSc patients with synovitis in the future.

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

### Papers

1. Varjú C, Péntek M, Lóránd V, Nagy G, Minier T, Czirják L. Musculoskeletal involvement in systemic sclerosis: an unexplored aspect of the disease. *J Scleroderma Relat Disord* 2017;2:19-32
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