Sensitivity to change of joint count composite indices in 72 patients with systemic sclerosis

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ABSTRACT

Objective. *We validated the responsiveness of joint count composite indices (JCCIs) in 72 patients with systemic sclerosis (SSc).*

Methods. *Changes in Disease Activity Score of 28 Joints using ESR and CRP (DAS28-ESR, DAS28-CRP), Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) were evaluated in a one-year follow-up study. Charts of patients including swollen/tender joint counts, laboratory signs of inflammation, and visual analogue scales referring to disease activity, severity and pain were also blindly categorised by two rheumatologists as improved, unchanged or deteriorated. These categories were used as references for the determination of effect size (ES) and standardised response mean (SRM).*

Results. *Articular inflammation improved in 15, deteriorated in 12, and remained unchanged in 45 (63%) patients with SSc based on the concordant opinion of two clinical investigators. All four JCCIs were sensitive to changes (ES>1; SRM>1). The correlation between changes in JCCIs and the physicians' evaluation was high (r >0.68; p<0.001). Arthritis was predominantly prone to change in patients with high JCCIs, impaired functional status, anti-RNA polymerase III antibodies and patients on DMARD therapy. Synovitis was more prevalent in patients with early diffuse SSc, and tended to improve during the follow-up.*

Conclusion. *All four JCCIs were sensitive to changes, if tender/swollen joints were present at baseline. Articular inflammation was most prone to change in patients with high JCCIs, impaired functional status and already decreased health-related quality of life at baseline.*

Introduction

Systemic sclerosis (SSc) is a connective tissue disease, affecting the internal organs, skin, and the musculoskeletal system. The clinical presentation is remarkably variable (1). Although lung and heart involvement are the leading causes of death in SSc patients (2-4), musculoskeletal involvement – in particular arthritis and joint contractures – has also been identified as a poor prognostic factor (5). Furthermore, synovitis is a predictor of progressive skin and lung involvement (6, 7). The prevalence of synovitis and joint contractures was estimated to be 18% and 31%, respectively (5, 8). Data from our single tertiary care centre showed that the prevalence of any contracture (defined as more than a 25% decrease in the range of motion in any of the joint axes) was 82% (9).

Arthritis predominantly affects the joints of the hands and usually appears early in the disease course of SSc (1, 8, 10-12), resulting in contractures which are one of the primary causes of disability and poor quality of life in patients with SSc (13-15). The newly developed Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) includes joint contractures as part of musculoskeletal damage (16). Conversely, the revised European Scleroderma Trials and Research Group Activity Index (EUSTAR-AI) does not contain arthritis as part of disease activity and therefore the current activity index may underestimate the importance of joint involvement in SSc (10).

In order to improve the assessment and follow-up of joint involvement in SSc, in our previous cross-sectional single-centre study we have partially validated the Disease Activity Score of 28 Joints using erythrocyte sedimentation rate (DAS28-ESR), the Disease Activity Score of 28 Joints using C-reactive

protein (DAS28-CRP), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) (12). These four particular joint count composite indices (JCCIs) were originally developed for patients with rheumatoid arthritis (RA), in order to allow global assessment and follow-up of disease activity (17).

During the validation process, we tested truth, discrimination and feasibility of these JCCIs according to the Outcome Measures in Rheumatology (OMERACT) filter (12). DAS28-ESR showed the best construct validity, discrimination and reliability among the four investigated JCCIs. Out of the four JCCIs, only CDAI failed to discriminate between subgroups based on the European Scleroderma Study Group Activity Index (EScSG-AI) (12).

As a further step, in the current study, we aimed to investigate the responsiveness and estimate the minimal important difference of these JCCIs in patients with SSc using the one-year follow-up data of the same SSc and RA patient cohorts.

Patients and methods

Patients

Seventy-seven patients fulfilling the 2013 ACR/EULAR SSc classification criteria (18) and 40 patients with RA satisfying the 2010 ACR/EULAR RA classification criteria (19) were enrolled into the study from the Department of Rheumatology and Immunology at the University of Pécs, Hungary. Cohort enrichment was performed to increase the rate of patients with early disease (disease duration ≤4 years) and diffuse cutaneous SSc (dcSSc). Disease duration was dated from first non-Raynaud's sign or symptom. 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). Fifty dcSSc and 27 limited cutaneous SSc (lcSSc) were enrolled, with a mean age of 56.3±11.8 years (± SD), and a mean SSc duration of 10.5±9.5 years. Baseline characteristics of the patients have been reported previously (12).

During the one-year follow-up, out of the 77 patients with SSc four patients died and one patient was lost to follow-up. Seventy-two patients, 46 with dcSSc and 26 with lcSSc, 62 females and 10 males, were re-evaluated after one year. Their mean age was 57.2±12.0 years with a mean SSc duration of 11.1±8.6 years.

The control group consisted of 40 patients with RA (36 females and 4 males, 24 had anti-citrullinated peptide antibodies). Their mean age was 59.3±8.1 years, and mean RA duration was 15.2±9.1 years. One patient was lost to follow-up, and one patient had missing data regarding disease activity. Thirty-eight patients with RA (34 females, mean age: 60.3±7.9 years, disease duration: 16.7 ±9.1 years) completed the one-year follow-up visit.

Methods

DAS28-ESR, DAS28-CRP, SDAI and CDAI were investigated regarding sensitivity to change. Overall disease activity was evaluated using the EScSG-AI (20), its recently modified version, the revised EUSTAR-AI (10) and the Modified Scleroderma Activity Index (21), which was also derived from the EScSG-AI.

To characterise disability, joint damage and hand function of patients with SSc and RA, the Hand Mobility in SSc scale (HAMIS) (22), the Health Assessment Questionnaire Disability Index (HAQ-DI), the Cochin Hand Function Scale (CHFS) (23), the Quick Questionnaire of the Disability of the Hands, Arms and Shoulders (QDASH) (24), the Hand Anatomic Index (25), the Delta finger-to-palm distance (26) and the 28 contracture count were assessed in addition to the JCCIs in question, as previously described (12).

Two experienced rheumatologists (LC and VL) scored the change in articular inflammation on a 5-point Likert-scale (major improvement, minor improvement, no change, minor deterioration, major deterioration) by blinded comparison of baseline and one-year follow-up charts. In addition to basic patient characteristics (age, disease duration, gender, disease subset) the anonymous patient charts included joint tenderness and swelling counts, inflammatory laboratory parameters (ESR, CRP, white blood count) and visual analogue scales reflecting global SSc disease activity, pain, joint pain and articular inflammation (12).

The intraclass correlation of the two physicians' blinded evaluation of change of articular inflammation, based on the charts was 0.872. In cases of disagreement (n=8), the two evaluators (LC, VL) discussed the activity data and reached a consensus. The originally formulated major (n=8) and minor improvement (n=7) categories were merged into one single 'improved' group, similar to the minor (n=7) and major (n=5) 'deteriorated' groups. For all further analyses, these three particular groups ('improved' /15/, 'no change' /45/, and 'deteriorated' /12/) were used.

The responsiveness of the JCCIs was also assessed after selecting patients with active joint disease (n=42) based on the recommendations of Clements et al. (HAQ-DI≥1.0, CHFS ≥10 and/or 28-tender joint count (TJC) ≥6) (27).

Patients with RA were also similarly categorised. The clinically minimal important difference estimate of DAS28-ESR was used for this purpose (28). RA patients with a change of DAS28-ESR less than 1.2 were assigned in the no change group (n=23); improvement was defined as a decrease of DAS28-ESR greater than 1.2 (n=9); while patients with an increase of DAS28-ESR larger than 1.2 were categorised in the group of deterioration (n=6).

All patients gave their informed written consent to the study, which was conducted according to the Declaration of Helsinki and 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).

Statistical analysis

Construct, structural, content and discriminant validity of the indices was retested using the one-year follow-up data of patients according to the OMERACT filter with the same statistical methods as the baseline data were

evaluated in our previous work (12). The SSc subgroups were compared by Chi-squared test or Fisher's exact test in the case of categorical variables and by Mann-Whitney U-test in the case of continuous variables.

To evaluate the responsiveness of the JCCIs, effect size (ES) and standardised response mean (SRM) were calculated. ES is the mean change of each JCCI – from baseline to the follow-up visit – divided by the standard deviation of the baseline JCCI value. SRM is the mean change of each JCCI divided by the standard deviation of the change from baseline to follow-up (29-32). Magnitude of responsiveness is compared using absolute values of ES and SRM, while the positive or negative sign shows the direction of change (33-34).

The minimal important difference cut-off values of the JCCIs were calculated using the receiver operating characteristic curve analysis and calculation of the Youden-index (35). The receiver operating characteristic was stratified according to the blinded evaluation of the change in joint inflammatory activity.

The data were analysed using SPSS software (v. 22.0) for Windows.

Results

A strong correlation was found between the physicians' blinded assessment of change in articular inflammation and all four clinical JCCIs (Table 1). Change of the JCCIs also showed significant correlation with change of CRP, ESR, but not with the Modified Rodnan Skin Score (mRSS) (Table 1). Out of the four JCCIs only the change of DAS28-ESR correlated with change of the EScSG-activity index (Table I).

Change of the JCCIs did not correlate with change of measures of disability (HAQ, Overall-VAS, CHFS, QDASH, HAMIS) (Table I) and damage (Delta finger-to-palm distance, Hand Anatomic Index, 28 contracture count) (data not shown).

All investigated JCCIs showed strong correlation with VASs of joint pain (rho: 0.518-0.734). Regarding the influence of the other potential sources of pain, no significant differences were found in the average values of JCCIs of subgroups based on the presence or absence of digital ulcers (n=15 *vs.* n=62 at baseline; n= 9 *vs.* 63 at follow-up visit, respectively; data not shown).

Assessment of responsiveness

Small mean change of JCCIs was found over a year in the entire SSc cohort (n=72), resulting in small absolute values of ES (<0.07) and SRM (<0.09) regarding all four JCCIs. When only patients with active baseline joint disease (HAQ-DI≥1.0, CHFS ≥10 and/or TJC≥6) according to Clements *et al.* (27) were included in the calculation (n=42), absolute values of ES (<0.12) and SRM (<0.13) of the JCCIs were larger, but still small. However, responsiveness of the JCCIs in the SSc subgroups based on physicians' blinded evaluation was good. ES and SRM were -0.98 to -1.18 and -1.08 to -1.37 in the improved group, 1.08 to 1.78 and 1.27 to 2.26 in the deteriorated group, respectively (Table II). In the whole RA cohort (n=38) the ES (<0.19) and

Table I. Correlations of joint count composite indices with different measures in patients with systemic sclerosis.

Systemic sclerosis (SSc) n=72	1 year follow-up visit				Change from baseline to 1 year follow-up				
	DAS28 ESR	DAS28 CRP	SDAI	CDAI	Change in articular inflammation§	DAS28 ESR	DAS28 CRP	SDAI	CDAI
Change in articular inflammation§	NA	NA	NA	NA	-	**0.686****	**0.718****	**0.760****	**0.751****
C-reactive protein (CRP)	**0.430****	**0.455****	**0.331****	0.228	**0.447****	**0.523****	**0.611****	**0.610****	**0.569****
ESR	**0.566****	**0.267***	**0.237***	0.178	**0.241***	**0.551****	**0.357****	**0.378****	**0.358****
EScSG-AI	**0.302***	0.212	**0.279***	**0.283***	0.079	**0.238***	0.158	0.137	0.121
MSAI	**0.353****	**0.258***	**0.322****	**0.324****	0.090	0.204	0.190	0.151	0.123
EUSTAR-AI	0.110	0.097	0.112	0.097	0.142	0.217	0.123	0.155	0133
HAQ-DI	**0.379****	**0.401****	**0.423****	**0.437****	**0.275***	0.166	0.187	0.195	0.193
Fatigue-VAS	**0.531****	**0.513****	**0.538****	**0.561****	0.222	**0.280***	**0.235***	**0.267***	**0.263***
Raynaud-VAS (SHAQ)	**0.458****	**0.478****	**0.488****	**0.468****	**0.308****	**0.245***	0.204	0.185	0.166
Overall-VAS (SHAQ)	**0.359****	**0.413****	**0.446****	**0.458****	0.033	0.114	0.083	0.062	0.055
Pain-VAS (HAQ)	**0.628****	**0.632****	**0.679****	**0.696****	**0.247***	0.196	0.209	0.225	0.219
Joint pain-VAS	**0.657****	**0.667****	**0.714****	**0.734****	**0.380****	**0.306****	**0.368****	**0.367****	**0.353****
Cochin Hand Function Scale	**0.250***	**0.285***	**0.312****	**0.326****	0.103	0.174	0.075	0.054	0.045
QDASH	**0.453****	**0.463****	**0.489****	**0.503****	0.131	0.179	0.216	0.178	0.174
Hand mobility in SSc scale	0.086	0.105	0.127	0.140	0.074	0.164	0.101	0.057	0.042
SF36-PCS	**-0.491****	**-0.462****	**-0.479****	**-0.485****	-0.055	-0.211	-0.231	-0.217	-0.210
SF36-MCS	-0.187	-0.189	-0.191	-0.194	-0.069	-0.150	-0.110	-0.105	-0.103
Modified Rodnan Skin score	-0.076	-0.116	-0.115	-0.130	0.132	0.178	0.151	0.153	0.151

Spearman's correlation coefficients (rho) are displayed in the table. **p<0.01; *p<0.05.

§Change of arthritis in patients with SSc, blindly assessed by two rheumatologists using patient charts (ordinal variable with 3 possible values on a Likert scale: improved, no change and deteriorated).

DAS28-ESR: Disease Activity Score of 28 Joints using ESR; DAS28-CRP: DAS28 using CRP; SDAI: Simplified Disease Activity Index; CDAI: Clinical DAI; EScSG-AI: European Scleroderma Study Group Activity Index; MSAI: Modified Scleroderma Activity Index; EUSTAR-AI: European Scleroderma Trials and Research Group Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index; SHAQ: Scleroderma-HAQ; QDASH: Quick Questionnaire of the Disability of the Hands, Arms and Shoulders; SF36: Short Form Health Survey, PCS: Physical Component Summary; MCS: Mental Component Summary; NA: not applicable.

Table II. Responsiveness of joint count composite indices in systemic sclerosis (n=72).

	Change in articular inflammation* (number of patients)	Joint count composite indices mean (SD)			Data of responsiveness	
		Baseline	1 year follow-up	Change over 1 year	Effect size	Standardised response mean
		All patients (n=72)				
DAS28-ESR	improved (n=15)	4.13 (1.32)	2.85 (1.48)	-1.29 (1.16)	-0.98	-1.11
	no change (n=45)	2.43 (1.32)	2.53 (1.28)	0.09 (0.70)	0.07	0.13
	deteriorated (n=12)	3.54 (1.05)	4.71 (1.13)	1.17 (0.58)	1.11	2.03
DAS28-CRP	improved (n=15)	3.92 (1.26)	2.54 (1.40)	-1.38 (1.01)	-1.10	-1.37
	no change (n=45)	2.04 (1.08)	2.07 (1.07)	0.03 (0.57)	0.03	0.06
	deteriorated (n=12)	2.90 (1.01)	3.99 (1.10)	1.09 (0.61)	1.08	1.79
SDAI	improved (n=15)	19.3 (10.7)	8.3 (9.8)	-11.1 (9.5)	-1.04	-1.17
	no change (n=45)	5.2 (8.5)	5.1 (8.6)	-0.1 (2.4)	-0.01	-0.05
	deteriorated (n=12)	10.8 (7.1)	21.3 (12.6)	10.5 (7.8)	1.48	1.35
CDAI	improved (n=15)	18.5 (9.8)	8.0 (9.7)	-10.5 (8.7)	-1.07	-1.20
	no change (n=45)	4.9 (8.6)	4.8 (8.6)	-0.1 (2.2)	-0.01	-0.05
	deteriorated (n=12)	10.6 (7.1)	20.8 (12.7)	10.2 (8.0)	1.44	1.27
		Patients with arthritis at baseline (n=42)**				
DAS28-ESR	improved (n=13)	4.37 (1.17)	3.03 (1.43)	-1.34 (1.24)	-1.14	-1.08
	no change (n=19)	3.02 (1.46)	2.44 (1.34)	-0.1 (0.65)	-0.07	-0.16
	deteriorated (n=10)	3.7 (1.07)	3.1 (0.93)	1.28 (0.57)	1.20	2.26
DAS28-CRP	improved (n=13)	4.14 (1.2)	2.74 (1.4)	-1.41 (1.08)	-1.18	-1.3
	no change (n=19)	2.44 (1.34)	2.42 (1.34)	-0.02 (0.63)	-0.02	-0.03
	deteriorated (n=10)	3.1 (0.93)	4.32 (0.81)	1.22 (0.59)	1.31	2.07
SDAI	improved (n=13)	20.9 (10.62)	9.44 (10.06)	-11.46 (10.19)	-1.08	-1.13
	no change (n=19)	8.54 (11.59)	8.16 (11.75)	-0.39 (2.52)	-0.03	-0.15
	deteriorated (n=10)	12.26 (6.79)	24.32 (11.49)	12.06 (7.63)	1.78	1.58
CDAI	improved (n=13)	19.95 (9.69)	9.17 (9.94)	-10.78 (9.38)	-1.11	-1.15
	no change (n=19)	8.28 (11.62)	7.92 (11.77)	-0.37 (2.38)	-0.03	-0.15
	deteriorated (n=10)	12.08 (6.71)	23.8 (11.69)	11.72 (7.91)	1.75	1.48

*Consensus of two independent rheumatologists' assessment of arthritis change using anonym patient charts.
**Tender joint count of 28 joints ≥ 6. HAQ-DI ≥1.0, Cochin Hand Function Scale ≥10 suggested by Clements *et al*. (27), see in part of Methods.
DAS28-ESR: Disease Activity Score of 28 Joints using erythrocyte sedimentation rate; DAS28-CRP: DAS28-using CRP; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; SD: standard deviation; HAQ-DI: Health Assessment Questionnaire Disability Index.

SRM (<0.19) values were also low regarding the JCCIs.

Assessment of minimal important difference

The receiver operating characteristic analysis of patients who deteriorated vs. no deterioration resulted in area under the curve values above 0.91, and the receiver operating characteristic analysis of patients with improvement *versus* no improvement led to area under the curve values above 0.88. Minimal important difference for deterioration was 0.52, 0.27, 2.15 and 2.05 for DAS28-ESR, DAS28-CRP, SDAI and CDAI, respectively. Minimal important difference for improvement was -0.55, -0.78, -4.63 and -5.65 for DAS28-ESR, DAS28-CRP, SDAI and CDAI, respectively.

Clinical comparison of subgroups based on changes in articular inflammation

Comparison of SSc subgroups based on physicians' opinion of changes in symptoms of articular inflammation is shown in Table III.

A significantly higher proportion of patients had dcSSc among patients with improved articular inflammation compared to the deteriorated group. Patients whose articular inflammation deteriorated had significantly longer disease duration than those who improved or had no change (Table III).

All patients with anti-RNA polymerase III antibodies (anti-RNAP III) who improved during follow-up were taking DMARDs. Similarly, in cases with anti-topoisomerase I antibodies, 6 out of 7 patients, whose articular inflammation improved, were also on DMARD-treatments (methotrexate, azathioprine, leflunomide, cyclophosphamide, mycophenolate mofetil or antimalarials) during the study period (Table III). Conversely, no patients with anticentromere autoantibodies (ACA) improved (Table III), however, 64% (n=14) of ACA positive patients (n=22) did not have any tender or swollen joints at baseline. Moreover, the proportion of ACA positive patients taking DMARDs was only 27%. Patients on glucocorticoid monotherapy did not show significant articular improvement during the follow-up (n=6). Patients without change of arthritis had significantly lower baseline JCCI values compared to patients with im-

Table III. Subgroups of patients with systemic sclerosis (SSc) based on one-year change in arthritis symptoms.

Demographic and baseline characteristics	§Experts' evaluation of change in arthritis			Statistical comparison		
	improved (I) n=15	no change (N) n=45	deteriorated (D) n=12	I *vs*. N	I *vs*. D	N *vs*. D
Gender, males, n	3 (20%)	7 (16%)	0	0.700	0.231	0.325
Age, mean years (SD)	59.2 (8.5)	53.7 (13.2)	61.5 (10.4)	0.068	0.533	**0.036***
Disease duration, mean years, (SD)	8.3 (10.2)	9.3 (7.9)	15.4 (7.8)	0.724	0.050	**0.028***
BMI, (kg/m^2) median (LQ;UQ)	29.5 (27.1; 33.4)	25.0 (20.5; 28)	28.4 (25.4; 33.1)	**0.002**$^{\$}$	0.614	0.**011**$^{\$}$
Diffuse cutaneous SSc, n	13 (87%)	29 (64%)	4 (33%)	0.192	**0.007****	0.052
Anti-centromere antibody, n	0	15 (33%)	5 (42%)	**0.013****	**0.010****	0.736
Anti-topoisomerase, n	7 (47%)	17 (38%)	2 (17%)	0.543	0.217	0.301
Anti-RNAP III RP 11, n	7 (47%)	6 (13%)	4 (33 %)	**0.008**$^{\$}$	0.196	0.696
Anti-RNAP III RP 155, n	7 (47%)	8 (18%)	3 (25%)	**0.029**$^{\$}$	0.424	0.686
Rheumatoid factor (n=51), n	3 (23%)	10 (33%)	4 (50%)	0.720	0.346	0.433
ESR mm/h, median (LQ; UQ)	12 (8; 16)	15 (7; 24)	20 (9; 27)	0.567	0.456	0.524
CRP mg/l, median (LQ; UQ)	2.5 (1.4; 9.7)	2.2 (1.0; 3.9)	1.5 (0.8; 2.4)	0.222	0.053	0.232
DMARD therapy¶, n	13 (87%)	22 (49%)	4 (33%)	**0.010**$^{\$}$	**0.004**$^{\$}$	0.336
Glucocorticoids, n	2 (13%)	10 (22%)	3 (25%)	0.456	0.438	0.556
Muscle weakness$^{¥}$, n	11 (73%)	15 (33%)	6 (50%)	**0.007**$^{\$}$	0.257	0.327
Results of tests, median (lower; upper quartiles: LQ; UQ)						
Modified Rodnan Skin Score	18 (12; 25)	16 (9; 23)	8 (6; 16)	0.252	**0.008**$^{\$}$	**0.030**$^{\$}$
Morning stiffness, minutes	15 (5; 30)	0 (0; 10)	15 (6; 44)	**0.003**$^{\$}$	0.863	**0.005**$^{\$}$
28 tender joint count	10 (5; 12)	0 (0; 1)	6 (2; 9)	**0.000**$^{\$}$	0.082	**0.000**$^{\$}$
28 swollen joint count	3 (1; 5)	0 (0; 0)	0 (0; 2)	**0.000**$^{\$}$	**0.013**$^{\$}$	0.272
DAS28-ESR	4.1 (3.4; 4.6)	2.4 (1.6; 2.8)	3.6 (2.8; 4.3)	**0.000**$^{\$}$	0.262	**0.002**$^{\$}$
DAS28-CRP	3.7 (3.1; 4.9)	1.7 (1.3; 2.2)	3.0 (2.0; 3.5)	**0.000**$^{\$}$	**0.028**$^{\$}$	**0.007**$^{\$}$
SDAI	18 (11; 22)	3 (1; 4)	10 (4; 16)	**0.000**$^{\$}$	**0.025**$^{\$}$	**0.003**$^{\$}$
CDAI	18 (10; 22)	2 (1; 4)	10 (4; 16)	**0.000**$^{\$}$	**0.026**$^{\$}$	**0.002**$^{\$}$
EUSTAR-AI	2.5 (1.5; 4.1)	2.5 (1.6; 3.8)	1.8 (1.3; 2.5)	0.841	**0.051**	**0.029**$^{\$}$
HAQ-DI	1.13 (0.63; 1.63)	0.63 (0; 1.19)	0.94 (0; 1.69)	**0.022**$^{\$}$	0.291	0.539
Hand Mobility in SSc scale	7 (4; 8)	5 (2; 9)	4 (2; 5)	0.269	**0.042**$^{\$}$	0.461
Cochin Hand Function Scale	10 (4; 24)	5 (1; 18)	9 (2; 15)	0.113	0.340	0.746
QDASH	48 (32; 57)	20 (7; 35)	39 (33; 51)	**0.007**$^{\$}$	0.418	**0.009**$^{\$}$
SF36 PCS	31 (23; 37)	41 (34; 50)	33 (23; 40)	**0.015**$^{\$}$	0.884	**0.023**$^{\$}$
SF36 MCS	48 (34; 56)	53 (39; 60)	48 (37; 62)	0.253	0.591	0.953

§Change in arthritis in patients with SSc, blindly assessed by two rheumatologists using patient charts.
$p<0.05$ values represent statistically significant results by *Independent t-test, **Fisher's exact test, §Chi^2-Test or $Mann-Whitney U-test.
¥according to patient's complaint.
SD: standard deviation; BMI: body mass index; Anti-RNAP III RP11/RP155: anti-RNA-polymerase III positive by immunoblot RP11 or RP155; ¶DMARDs: chloroquin/methotrexate/leflunomide/cyclophosphamide/ mycophenolate mofetil; DAS28-ESR: Disease Activity Score of 28 Joints using erythrocyte sedimentation rate; DAS28-CRP: DAS28 using CRP; SDAI: Simplified Disease Activity Index; CDAI: Clinical DAI; EUSTAR-AI: European Scleroderma Trials and Research Group Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index; QDASH: Quick Questionnaire of the Disability of the Hands, Arms and Shoulders; SF36: Short Form Health Survey; PCS: Physical Component Summary, MCS: Mental Component Summary.

provement or deterioration. (Table III). As with JCCI values, HAQ-DI and qDASH showed a similar trend for the aforementioned subgroups (Table III).

Articular inflammation was significantly more prone to change in obese SSc patients, than in patients who were within the normal BMI range (Table III).

Comparing the three SSc subgroups based on changes of articular inflammation (improved, no change, deteriorated), there were no significant differences concerning other baseline clinical parameters (lung function tests, left ventricle ejection fraction, global disease activity, structural hand damage) (data not shown).

Assessment of validity at one-year follow-up

Regarding construct validity, DAS28-ESR, DAS28-CRP, SDAI and CDAI showed significant correlation with measures of global disease activity (EScSG-AI, MSAI) and disability (HAQ, VAS-overall, QDASH, CHFS), both at baseline (12) and at follow-up visit (Table I). There was no correlation between the JCCIs and the mRSS, Hand Anatomic Index, Delta finger-to-palm distance, and 28 contracture count (data not shown).

Concerning content validity, less than 15% of the patients had the lowest possible JCCIs, and none of them reached the highest possible value.

Variables reflecting disease activity, joint involvement, quality of life, joint structural damage, functional musculoskeletal indices and JCCIs were included in principal component analysis. In the principal component analysis, 54% of the original information was present in the first two components. All four JCCIs as well as HAQ, VAS-fatigue, CHFS, QDASH, joint pain-VAS and the physical component of short form health survey fell into the first component. Measures reflecting structural damage including hand anatomic index, delta finger-to-palm distance, and 28 contracture count belonged to the second component.

Regarding structural validity, principal

component analysis was performed. DAS28-ESR and CDAI were unidimensional, their components being grouped into a single factor, which explained 53% and 73% of their variance, respectively. However, DAS28-CRP and SDAI were grouped into two factors, CRP solely being assigned into the second factor. The two factors explained 78% and 79% of the variance of DAS28-CRP and SDAI, respectively.

Concerning discriminant validity, at one-year follow-up a significant difference was found between DAS28-ESR values of patients with ESR ≤30 mm/h compared to those with ESR>30 mm/h (p=0.004), as well as DAS28-ESR and DAS28-CRP values between SSc patients with CRP≤5mg/l and >5mg/l (p=0.045, p=0.038, respectively). All four joint assessment scores differentiated between SSc patients with HAQ-DI<1 compared to those with HAQ-DI≥1 (p<0.001). JCCIs did not discriminate between dcSSc and lcSSc subgroups, as well as between subgroups based on global disease activity (EUSTAR-AI ≥2.5 *vs*. EUSTAR-AI <2.5), (data not shown).

Discussion

In our previous cross-sectional study, we demonstrated that DAS28-ESR, DAS28-CRP, SDAI and CDAI were valid measures for assessing arthritis in SSc. Several domains of the OMERACT filter requirements including construct, content and discriminant validity as well as reliability and feasibility were sufficiently fulfilled (12). In the present study, we addressed the question of the responsiveness of JCCIs during a one-year follow-up study. We showed that JCCIs were sensitive to change in SSc patients with arthritis. Since we used cohort enrichment for patients with dcSSc and short disease duration, the proportion of cases without arthritis symptoms was probably lower than in unselected SSc cohorts. In our study, arthritis was predominantly prone to change over time in SSc patients with high JCCIs, impaired functional state and decreased health related quality of life at baseline.

The articular inflammation was significantly more prone to change in obese SSc patients than in patients who were within the normal BMI range might be explained by the fact that obesity by itself can cause a slight generalised inflammatory state (37), and may interfere with the inflammation of the joints. Synovitis, particularly joint swelling, was more frequently present in the early phase of the disease predominantly in patients with dcSSc, and these particular patients tended to improve during the one-year follow-up while on DMARD therapy (Table III). Follow-up of joint complaints seems to be beneficial in this particular subgroup of SSc patients. Articular inflammation was less prone to change in patients with absent or mild joint symptoms. Our results therefore confirm the previous suggestion by Clements *et al*. that baseline musculoskeletal disease affects the degree of response (27), and patients without the signs of arthritis, or only a minimal degree of synovitis, may not be the optimal candidates for the follow up of articular inflammation by the evaluation of JCCIs.

As previously suggested by Clemens *et al*. (27), the selection criterion in clinical trials for the evaluation of inflammatory joint involvement should be based on some degree of arthritis combined with functional impairment scores (HAQ-DI≥1.0, CHFS≥10 and/or TJC≥6) (27). However, the most reported scoring system assessing tenderness and swelling in 8 joints failed to show a significant change with treatment in four RCTs (27, 38-41) The possible explanation may be that the number of investigated joints was low, therefore we suggest the evaluation of 28 joints.

The JCCIs and also changes in JCCIs did not correlate with instruments representing irreversible joint damage. The Hand Anatomic Index, the Delta finger-to-palm distance, and the 28 contracture-count did not show any correlation with the JCCIs either at baseline or at one-year follow-up (data not shown) indicating that these JCCIs predominantly reflect articular inflammation. Furthermore, change in HAQ-DI values and changes in the JCCIs did not correlate (Table I). However, HAQ-DI values showed correlations with the JCCIs at baseline and also at follow-up, indicating that this particular instrument also measures some disability caused by articular inflammation (Table I).

As shown in a small previous study (n=7), the 28 tender joint count had an excellent inter-observer (0.97) and intra-observer reliability (0.99) in patients with SSc. Intra-observer reliability of the 28 swollen joint count was also good (0.71), while inter-observer reliability was poor (0.24) (42).

The high number of SSc patients with no (n=45) or only a minor change (n=14) assessed by the two independent investigators may partially explain the small ES and SRM of the JCCIs. ES and SRM values of the JCCIs became only slightly better when only patients with articular inflammation (27) at baseline were included (Table II). Mean change, ES and SRM can be most effectively measured in a patient cohort assumed to change in the same direction, either improving or deteriorating. Accordingly, ES and SRM values were also tested in SSc subgroups based on blinded assessment of changes in articular inflammation. The JCCIs showed an excellent responsiveness in subgroups with either deteriorating or improving articular inflammation. The JCCIs also showed comparable responsiveness when only patients with active joint disease at baseline were included in these subgroups (Table II). The responsiveness values of the investigated four JCCIs were comparable to each other (Table II).

In our study the number of tender joints was much higher compared to the swollen joint counts (Table III), indicating that arthritis may be less pronounced in SSc compared to RA and besides the inflammatory process, other mechanisms may also contribute to the joint count scores. This theory is also supported by the mentioned small study that showed no correlation between the joint ultrasound findings and the number of tender/swollen joint counts (42). According to previous findings, the severity of Raynaud's phenomenon was associated with the development of erosive joint changes in SSc (43, 44). These findings suggest that ischaemia caused by micro/macroangiopathy can

be a contributing factor to the increased tender joint count, and consequently to the elevated JCCIs (44).

A recent Spanish investigation (45) has shown that SSc patients with anti-RNAP III had more frequently developed arthritis and contractures compared to those, who were anti-RNAP III negative. In this study we could not count significant difference in the average values of JCCIs between groups with or without anti-RNAP III (data not shown). However, we found that most of anti-RNAP III positive cases with high JCCIs at baseline taking DMARDs showed an improvement in JCCIs during a one-year follow-up (data not shown). To the best of our knowledge, the impact of DMARD treatment on arthritis in anti-RNAP III cases has not been previously reported, although we have to emphasise that the number of our cases was low (Table III). On the other hand, our study showed that glucocorticoid treatment did not have a long lasting effect on arthritis in patients with SSc.

The main limitation of our study is the relatively small sample size. We must also note that there were only 20 patients (15 dcSSc/5 lcSSc) with early disease (disease duration ≤4 years at baseline) in our SSc cohort. Due to the small sample size and the cohort enrichment performed at enrolment of patients with SSc our minimal important difference estimates should be used with caution.

In summary, DAS28-ESR, DAS28-CRP, SDAI, and CDAI showed good responsiveness in SSc patients with synovitis. SSc patients with early disease, significant baseline arthritis, and disability seem to be the most prone to changes over time. Similar to RA, our results indicate that changes in articular inflammation can be evaluated using the conventional JCCIs in patients with SSc. Further studies are required to make a conclusion on whether increased JCCIs coincide with further progression of joint damage/contractures and whether they may be an appropriate instrument to measure outcomes in patients with articular inflammation. Cut-off values of remission and significant inflammation should be also defined, in future as well as evidence-based treatment strategies with DMARDs and targeted treatments in the different subsets of patients, in order to initiate the "treat-to-target" principles in this disease.

Take home messages

- Joint count composite indices show good responsiveness in scleroderma patients having tender and/or swollen joints.
- Improvement in joint count composite indices was most prevalent in patients with diffuse cutaneous scleroderma.
- Arthritis was most prone to change in cases with high joint composite indices at baseline.

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