INVESTIGATION OF MUSCULOSKELETAL DAMAGE AND HAND FUNCTION IN SYSTEMIC SCLEROSIS

Ph.D. thesis

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1. INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease affecting the skin, musculoskeletal system and internal organs by vascular lesions and fibrotic changes. End stage disease is characterized by obliterative vasculopathy and atrophy of the involved organs. Musculoskeletal manifestations of SSc include arthralgia, arthritis, tendinitis, contractures, myositis and symmetric deformation of the hands and the large joints.

SSc is a rare chronic disease, it is estimated that the new cases of scleroderma occur at of approximately 1,2 – 43 per million of the general population per year, and the prevalence is 4-341 /1 000.000. The incidence of scleroderma is higher in females than in males (3-6:1). The limited form of systemic sclerosis (lcSSc) has a strong female predominance, with a female-to-male ratio of 10:1. Another analysis showed that men tend to have diffuse cutaneous SSc disease (dcSSc) and women to have calcinosis.

Based on the skin involvement, limited and diffuse cutaneous SSc subsets are differentiated. Several environmental factors (viruses, solvents, chemicals) can play role in development of the disease. Among the chemicals the most frequent provoking factors are the organic dissolving agents, about in 1/5-1/6 of the patients'anamnesis, usually as work-related hazard. Polyvinil chloride, quartz crystal and certain drugs, e.g. bleomycine also play role as provoking factors.

Musculoskeletal involvement significantly influences quality of life both in patients with lcSSc and dcSSc. The most frequent symptoms are the symmetric hand arthritis, contractures and pain, which occur in 46-97% according the literature.

The early symptom of SSc beside of Raynaud's phenomenon is the pain of the hands due to erosive arthritis (synovitis and tenosynovitis), which causes narrowing of the articular space and decreasing range of motion (ROM) soon. Subcutaneous calcium deposition, ischemic digital ulcers, thickened fibrotic skin also lead to deterioration of the hand function. Proximal type of muscle weakness (mainly around shoulders and hips), elevated creatin-kinase (CK) also occur in SSc.

Department of Rheumatology and Immunology of the University of Pécs is a traditional terciary care centre of the patients with scleroderma. Recent years there was a large development in methods – both in the evolvement of outcome measureintruments and validation of these particular tools. However, despite the importance of musculoskeletal damage in SSc, there has been no clinical universally accepted tool to identify and quantify

musculoskeletal damage in SSc, with current tools assessing disease severity, activity or combined.

SSc is a chronic complex and heterogeneous disease. The change of disease activity and tissue damage of the involved internal organs and the musculoskeletal status should be monitored, as well the daily activities and the health related quality of life (HRQOL). SSc is a rare disease, therefore international cooperation is mandatory for the research of the pathophysiology and determination of the most effective therapy. For the internationally research universal investigation methods are very important, therefore the Hungarian cultural adaptation and validation of the international measures are mandatory.

During my work, SSc has become my favourite field. I was motivated to confirm with our results the practical experiences and the musculoskeletal associations with changing of the whole disease severity and the HRQOL.

The aim of my scientific studies was to investigate the effect of scleroderma for the musculoskeletal system, especially monitoring the changes of the hand functions and the HRQOL. Furthermore, we have cooperated with other Hungarian centre of rheumatology and rehabilitation to investigate the effects of the intensive complex physical therapy.

2. AIMS

2.1 Hungarian adaptation and psychometric validation of wellknown international questionnaires

Among our scleroderma patients, we performed the Hungarian adaptation and validation of the scleroderma-Health Assessment Questionnaire (sHAQ); and the Disabilities of the Arm, Shoulder and Hand (DASH) and its shorter variation, the QuickDASH self-assessment Questionnaire

2.2 A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis

The aim of this prospective clinical study was to perform a longitudinal study to observe the developments and changes of joint contractures, and assess their association with disease outcome. We examined subclasses of patients with SSc based on their skin involvement as well as length of their disease duration time.

2.3 Conducting research focusing on hand function

2.3.1 Comparison of the hand function of patients with systemic sclerosis and rheumatoid arthritis (RA)

We compared the hand function of the two diseases by giving details of the distribution of the involved and especially the inflamed joints. We were also analysed the associations of the clinical manifestations and the hand joint involvement of the patients with SSc and RA.

2.3.2 Examination the efficacy of intensive hand physical therapy in patients with systemic sclerosis

We performed a controlled clinical study to evaluate the efficacy of a three-week period of complex and intensive hand physical therapy on hand function in patients with SSc. The intensive hand-therapy included of stretching exercises, ergotherapy supplemented with thermal and mud baths, whirlpool therapy and soft tissue massage.

3. PATIENTS AND METHODS

3.1 Hungarian adaptation and psychometric validation of wellknown international questionnaires

The adaptation and psychometric validation of the scleroderma HAQ and the DASH test were performed in a same group of consecutive Caucasian patients with SSc. One hundred and sixteen women, 12 men, 87 with lcSSc and 41 with dcSSc were involved into this study, their mean age was 55.7±11.7 years (±SD), with a mean disease duration of 10.4±8.2 years from the first non-Raynaud's symptom.

3.1.1 Fries et al developed the **HAQ** in 1985, which has been used extensively in the measurements of rheumatic diseases. HAQ is important in both clinical practice and research studies. Steen and Medsger added five special questions and visual analogue scales (VAS) for the answers to the scleroderma HAQ, assessing Raynaud's phenomenon, digital tip ulcers, gastrointestinal and lung symptoms, and overall disease severity from the patient's perspective. The five VAS ask patients, how much these symptoms interfere with their daily activities. The original HAQ was adapted to Hungarian patients by Rojkovich B and co-workers in 1998. In this study we adapted only the five special questions and the VAS answers for the Hungarian patients with SSc. Each question should be answered proportionally between the two endpoints, "Not obstructed" and "Very severely obstructed," on a 15 cm horizontal VAS line. The value of the 15 cm VAS is given individually by

converting it proportionally to a value between 0 and 3: i.e., the value measured in cm from the origin is multiplied by 0.2. The sHAQ index is finally obtained by taking the points of the original HAQ 8 and the arithmetic mean of the 5 VAS values converted as above. The sHAQ index can range from 0 for best status to 3 for worst functional status. Each 15cm-VAS score should also be reported and monitored individually.

3.1.2 The main part of the **DASH questionnaire**, called "the DASH disability-symptom" contains 30 questions: 21 about the degree of difficulty in performing various physical activities, 5 regarding severity of symptoms of pain, tingling, weakness and stiffness, and 4 dealing with problems affecting social activities, work and sleep, and with psychological impact. The DASH also contains two optional 4-item parts concerning ability to work (DASH-W) and ability to perform sports, or play musical instruments (DASH-SM). Each item has 5 response choices (1-5) ranging from "nodifficulty" or "no symptom" to "unable to perform the activity" or "very severe symptom". The scores for all items are used to calculate final score ranging from 0 (no disability) to 100 (severest disability). If more than 10 percent of the items are left blank, then that part of the DASH is not calculated. The **QuickDASH** questionnaire is an abbreviated version of the DASH, containing only 11 of the questions in the DASH-General section, but the two optional sections, DASH-W and DASH-SM, remain unchanged.

The 5 additional questions from SHAQ, the translation of the DASH and QuickDASH abridged questionnaires from English and their adaptation to Hungarian culture are the subject of an internationally popular so-called "back and forth" translation method.

For psychometric examination of questionnaires we used the methodological recommendation so-called „OMERACT filter (Outcome Measures in Rheumatoid Arthritis Clinical Trials, Boers M. et al. in Journal of Rheumatology 1998;25:198-9). The methods („truth value", „discriminatory credibility test", "applicability") are detailed in the results.

3.2 A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis

One hundred and thirty-one consecutive Caucasian patients, 119 females and 12 males, 41 with dcSSc, 90 with lcSSc were included in the study. At baseline, their mean age was 55.9±11.6 years (±SD), with mean disease duration of 8.1±7.2 years from the first non-Raynaud's symptom. The mean follow-up time was 4.43±3.34 years.

The most important internal, skin and musculoskeletal clinical parameters were recorded according to a standard protocol. Based on physical examination, the peripheral joints'

movements of the patients were measured (using a goniometer - joint protractor). Joint contracture was detected when the normal range of motion (ROM) decreased by more than 25%. Serious contractures of the joints were diagnosed narrowing of more than 50% of the ROM of the particular joint. To measure and monitor the structural and functional damage of the hand joints, we used the delta-fingertip to palm index (delta FTP) and the Hand Anatomic Index (HAI). Both are simple and validated methods for patients with RA and SSc. Dynamometer was used for measuring the changes in muscle strength of the arms and hands. . An educational and clinical treatment program was repeated every 6 to 12 months during the three years of the study. For five days out of the week, patients received special physical therapy: respiratory training, physical therapy included joint mobilization, strengthening and stretching exercises for the hands, as well the spine as all peripheral joints.

3.3 Research focusing on hand function

3.3.1 Comparison of the hand function of patients with systemic sclerosis and rheumatoid arthritis

An observational cross-sectional study was conducted with quantitative and qualitative parameters. Our target group was 77 SSc patients (50 dcSSc, 27 lcSSc), 67 females and 10 males, their mean age was 56.3 ± 11.8 years (± SD) and mean disease duration was 10.5 ± 9.5 years. As control groups 40 patients with RA, 20 patients with primary Raynaud's syndrome, and 20 healthy subjects were studied. The RA group consists of 36 females, 4 males, their mean age was 59.3 ± 8.1 years and disease duration was 15.2 ± 9.1 years. The results of the revised Medsger severity scale for disease severity, the Disease Activity Scores by 28-joint counts (DAS28) and the Clinical Disease Activity Index (CDAI) values for joint activity were calculated. Contractures were examined for the affected joints. Muscle function and muscle strengths were tested bilaterally by a protocol so-called MMT8 method (Manual Muscle Testing), which measures muscle strength against manual resistance in 8 muscle groups. We also measured the objective clamping and pinching force using a Jamar® dynamometer to examine distal muscle groups and hand function. We also performed a power-based HAMIS (Hand Mobility in SSc) test to measure hand and wrist function. The structural and functional damage of the hand joints was examined by delta FTP (distance of finger to palm) and HAI (Hand Anatomic Index). Patients' proximal limb circumference values were also measured. The subjective data were collected using patient-filled questionnaires: QuickDASH, HAQ test and Cochin hand function scale.

3.3.2 Efficacy of intensive hand physical therapy in patients with systemic sclerosis

A prospective controlled follow-up study was conducted in collaboration with SSc patients of the Department of Rheumatology and Immunology of the University of Pécs, Hungary in cooperation with the Hospital of St. Andrew's Spa in Hévíz to investigate the long-term effect (after 6 months) of the 3-week hand rehabilitaion treatment period. The study group consisted of 31 patients with SSc (18 with dcSSc, 13 with lcSSc, their mean age was 59.7 ± 14.5 years /± SD/). Criteria of inclusion consisted of the presence of at least two hand joint-contractures as a manifestation of SSc.

Patients were consistently enrolled in the hand therapy group until the maximum number was reached, and then patients who met the inclusion criteria were enrolled in the control group until the end of the study. The therapy consisted of six different treatments: thermal bath (37-38 ° C, 30 minutes/day), therapeutic mud treatment on hands (42°C, 20 minutes/ day), whirlpool (37-38°C in mineral water, 20 minutes/day), therapeutic massage (30 minutes/occasion), ergotherapy (30 minutes: muscle stimulation, proprioceptive training, development of coordination and good motor abilities, improvement of self-care if needed), and physicaltherapy (30 minutes/day: isometric, isotonic and stretching exercises on the hands, completed with breathing exercises) 15 times in a 3-week period.

The control group consisted of 22 SSc patients, 9 with dcSSc and 11 with lcSSc, their mean age was 62.1 ± 8.4 years. The control group received similar therapy to their spine and large joints without being a subject to any treatment to the hands. In our clinic, patients were assessed 3-4 weeks before and 6 months after rehabilitation with a fully standardized protocol with their colleagues in Hévíz. As part of the protocol, there was a general medical examination, a physiotherapist's motion assessment: HAI, delta FTP, hand clamping force and pinch force measurement (Jamar® HandSet). DASH, HAQ, sHAQ, SF-36 and Cochin tests were also completed.

3.4 Statistical analysis

The distribution of values was evaluated using the Kolmogorov-Smirnov test. Changes in ROM degrees were analyzed using the Wilcoxon Ranking Test. The frequency of arthritis involvement in the subgroups was analyzed using the Mann-Whitney U test. The system of correlations was analyzed by Spearman's correlation coefficient. Multiple linear regression was applied to examine which factors influence changes in contracture numbers by stepwise selection. Statistical analyzes were performed using IBM SPSS Statistics v 20.0 (IBM Corporation Rate, New York, USA).

4. RESULTS

4.1 Adaptation to Hungary and psychometric validation of wellknown international questionnaires

4.1.1 Scleroderma Health Assessment Questionnaire (sHAQ)

4.1.1.1 Applicability: The adaptation of the sHAQ questionnaire to Hungary was started with pilot studies involving 20 SSc patients, 18 females, 2 males, with a mean age of 55.8 ± 8.7 years (± SD). After completing the questionnaire, the patients considered the questions unambiguous and did not propose any further changes as a result, the Hungarian-language sHAQ was finalized.

4.1.1.2 Concurrent, convergent and criterion validity: There were strong correlations between the HAQ-DI and sHAQ index and the parameters measuring musculoskeletal function, while there were weak correlations between HAQ-DI and sHAQ indices and the results of pulmonary and cardiac status or the skin conditions. The closest correlations were found between HAQ-DI or the sHAQ and Physical function scores of SF-36, while the weakest correlation was found between the Emotional role or Mental health topics of the SF-36 and the HAQ-DI or sHAQ.

4.1.1.3 Content validity: it was determined by examination of the "floor and ceiling effect". Only one patient had an index score of 0 (the best possible value) and no patient had a score of 3 (the worst possible). Therefore, it can be stated that the sHAQ index is able to follow minor changes in both improvement and worsening in SSc patients.

4.1.1.4 Structural validity: the analysis confirmed the one-dimensional character of the HAQ-DI and VAS properties by principal component analysis. The eigen value of the first factor was 3.37, which was a latent variable that contained 56% of the total variance for one year. One-dimensionality is evidenced by the fact that the eigen value of the possible next latent variable was significantly smaller (0.85). The latent variables showed linear correlation (rho = 0.6 and higher).

4.1.1.5 Discriminant validity: Patients with multiple organ affected had a worse sHAQ score than those with fewer organ manifestations ($p<0.001$). In the dcSSc subgroup, sHAQ and HAQ-DIs showed higher (worse) values compared to patients with lcSSc subgroup ($p<0.05$). Both HAQ-DI and sHAQ showed higher (worse) results in the case of skin ulcers, pronounced knee extensor muscle weakness, and hand contractions.

4.1.1.6 Reliability: In terms of reliability, the internal consistency of sHAQ did not change during adaptation to Hungary (Cronbach alpha: 0.91).

4.1.1.7 Examining reproducibility similarly to other studies, high intraclass correlation coefficients were calculated for both HAQ-DI (0.96) and sHAQ (0.91).

4.1.2 Validation of the DASH questionnaire in patients with systemic sclerosis

4.1.2.1 Applicability: 20 scleroderma patients completed the test within 7-14 minutes, who did not suggest further changes to the Hungarian-language test.

4.1.2.2 Psychometric assessment: all 128 patients completed the DASH-General section successfully, but 26.5% (34 patients) did not answer question 21 about their sex life. The optional DASH-W was completed by 37.5% of patients (48 persons: 34 in lcSSc, 14 in dcSSc). The optional DASH-Sport and Arts section was completed only by 6.3% of patients (8 persons).

4.1.2.3 Truth, concurrent validity: DASH score correlated with both SSc-HAQ (rho = 0.49) and SF36 Physical domains (rho = 0.89). The SF-36 had poor relationships with its Mental domains. The DASH-General and QuickDASH-General indices showed moderately strong, significant correlations with HAI (which representing the anatomical damage of the hands), and with the joint-tendon and muscle status index of the Medsger Severity Scale.

During the structural validity examination unidimensionality was also verified in the DASH and QuickDASH analyses.

4.1.2.4 Discriminant validity: the results of DASH-General, QuickDASH-General and DASH-W tests showed significantly higher values for the patients with hand or shoulder contracture compared to patient groups without these contractures; just as in patients with symmetrical polyarthritis compared to the group without polyarthralgia.

4.1.2.5 Reliability test: Cronbach alpha value, which shows the internal consistency of the questionnaire, was 0.94-0.96 after the Hungarian adaptation. In extreme values, when analyzing the floor-ceiling effect, 0 was found in only one patient in the DASH-General test, and in 3 patients in QuickDASH, while the worst value (100) was not found in any patient. DASH-W and DASH-SM 20.8% and 25%, respectively, showed 0, the best values.

4.1.2.6 Reproducibility were performed within a short period of time. Both questionnaires were medium to high reproducibility: ICC for DASH-General was 0.89 (95% CI 0.82-0.93), for QuickDASH it was 0.87 (95% CI 0.79-0.92).

4.1.2.7 Analyzing the sensitivity of the DASH indices to change, based on the change in HAQ-DI, the results of the DASH, QuickDASH, and SF-36 dimensions were divided into 3 groups: worse, unchanged, improving HAQ-DI. Similar to HAQ-DI, the DASH and QuickDASH-General indices showed a change in patients with a worsening condition, but

there was no significant improvement (decrease in score) in patients improving on the basis of HAQ-DIresults. The standard response mean (SRM) was 0.64 for patients with worsening, based on the change in HAQ-DI.

4.2 A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis

4.2.1 Presence of contractures in patients with SSc

During the three-year follow-up, with respect to peripheral joint involvement II. and III. MCP joints were the most frequently affected, with 73-82% of the 131 patients examined, having contractures in these joints (ROM <75%). The contracture of the flexion-extension range of the wrist was in 69-75% of patients and in 18-22% of patients in the direction of adduction-abduction. In the case of the shoulder joint, 50-49% of the patients had contracture on flexion-extension, 15-13% on adduction-abduction, and 11-9% on rotation. In theperipheral joints, between 15 and 17% of patients had knee contracture in the flexion-extension range of motion.

4.2.2 Comparison of dominant and non-dominant side

According to our results the anatomical and functional condition of the dominant hand was worse compared to the non-dominant side. At the third follow-up, the difference in the mean joint degree between the dominant and the non-dominant side in II. MCP was 5.8 ° ($p < 0.001$), in III. MCP joint, it was also 5.8 ° ($p < 0.001$), in II. PIP joint was 2.9 ° ($p = 0.058$), in III. PIP joint 4.7 ° ($p < 0.001$) and in the flexion-extension range of the wrist it was 6.4 ° ($p < 0.001$).

4.2.3 Analysis of contractures in different subsets of patients

Significantly more contractures were found in the dcSSc patient group than in the lcSSc subgroup, as well as in the anti-topo I positive patient group compared to the negative subgroup. The presence of ACA, RF, and anti-CCP antibodies was not associated with increased number of joint contractures in patients with SSc. Significantly more joint contractures were found in SSc patients with ILD than in non-pulmonary fibrosis patients. There was also a significant difference in the number of joint contractures between the group of patients with and without active finger ulcer, and between the positive and negative subgroups in subcutaneous calcinosis. No significant differences were found in the number of contractures between males and females, either in the subgroup with or without arterial pulmonary hypertension, and in the subgroups based on the presence of cutaneous hypo/hyperpigmentation. MRSS was higher ($p < 0.01$) in the group of patients with joint

contractures (median /quartiles/: 4.5 /3.25-11/) than in the subgroup without contractures (1.75 / 1.3-5-5) for all three study years.

No difference was found in the number of contractures (ROM <75%) in the subgroups with disease duration greater than 4 years or less. The median number of contractures in the subgroup of 52 patients with short illness (≤4 years) was 8 (6-11; 25-75% quartile), which is consistent with the 8 (6-13; 25-75% quartile) of the long-term (> 4 years) subgroup.

4.2.4 Clinical associations of development of joint contractures

In the baseline study, upper limb severe contractures (ROM <50%) were moderately, positively correlated with erythrocyte sedimentation (rho: 0.249, p <0.01), CRP (rho: 0.319, p <0.01), HAQ-DI (rho: 0.386, p <0.01) and with the score of DASH questionnaire (rho: 0.341, p <0.001). Similarly, the number of severe upper limb contractures was negatively correlated with lung FVC (rho: -0.251, p <0.05). We found this data for both the first and third year follow-up. Large joints of the lower limb were rarely affected (7.9%) and showed no significant association with inflammatory, cardiac and pulmonary involvement parameters. Functional index values (HAQ-DI, DASH) showed no significant changes in the 3-year follow-up study. The diffuse SSc subgroup with early disease (≤4 years, 17 patients) was the only exception whose HAQ-DI showed a slight improvement (p <0.05) in first and second follow-up, however this HAQ-DI value showed a deterioration in the third year follow-up. Based on multiple linear regression stepwise selection method changes in mRSS skin score, erythrocyte sedimentation, and EScSG Activity Index as independent variables were associated with an increase in total contracture count (ROM <75%) (p <0.05) in the first year follow-up.

4.2.5 Results of functional indices

Functional index values (HAQ-DI, DASH) showed no significant changes in the 3-year follow-up study. The diffuse SSc subgroup with early disease (≤4 years, 17 patients) was the only exception whose HAQ-DI showed a slight improvement (p <0.05) in first and second follow-up, however this HAQ-DI value showed a deterioration in the third year follow-up. Based on multiple linear regression stepwise selection method changes in mRSS skin score, erythrocyte sedimentation, and EScSG Activity Index as independent variables were associated with an increase in total contracture count (ROM <75%) (p <0.05) in the first year follow-up.

4.3 Research focusing on hand function

4.3.1 Comparison of the hand function of patients with systemic sclerosis and rheumatoid arthritis

Fifty percent of patients with SSc had no tender joints at all, a significant difference compared to the RA group, where 58% of patients reported pressure-induced joint pain ($p = 0.007$). In the SSc group the wrists, the MCP and PIP joints are most commonly affected. However, joint tenderness compared to swelling was significantly ($p < 0.05$) higher in the majority of the tested joints (shoulders, elbows, wrists, PIP joints) in the SSc group, whereas swelling was particularly rare in large joints. In both patient groups, II. and III. fingers were the most commonly affected. The distribution of joint swelling and tenderness was similar in both patient groups.

The hand anatomical index (HAI) of the healthy group and the Raynaud's syndrome patients did not differ significantly, nor did the values of the patients with SSc and RA. None the less, the values indicate that the SSc group has the worst HAI score, followed by RA patients with Raynaud's syndrome. Patients with scleroderma also had the worst ability for fist formation, the second worst for patients with RA, and finally those with Raynaud's syndrome.

Within the muscle strength measurement, the clamping and pinching force is given by the average of the two sides. The healthy group values are better than all groups and significantly different from the SSc ($p < 0.001$) and RA group ($p < 0.001$). Patients with RA have the weakest force and clamping force, followed by scleroderma and then Raynaud's syndrome. The results of the MMT8 bilateral manual muscle strength measurements on a scale of 10 also show significant differences between patient groups. The results for the healthy group did not differ significantly from the Raynaud's group. Force values were the weakest in RA.

Based on the summary of the questionnaires, the results of the HAQ indicate that there is a significant functional difference between scleroderma patients and RA patients ($p = 0.034$), SSc and healthy groups ($p < 0.001$), and between SSc and Raynaud's syndrome patients ($p = 0.011$). According to the evaluation, patients with RA had the worst functional status. The Cochin Hand Functional Test also found that the RA group had the most severe hand function impairment compared to other groups. The relationships and trends of the QuickDASH scores were the same as those described earlier for HAQ with the difference that there was no significant difference between the SSc and RA patient groups. Elements of the SF36 questionnaire for general health were calculated separately. When assessing general health, the SF-36 physical function component showed significant differences ($p < 0.05$) in the

scleroderma and RA groups compared to all three other study groups. The worst data had the RA patient group.

4.3.2 Efficacy of intensive hand physical therapy in patients with systemic sclerosis

The study group consisted of 31 SSc patients and the control group 22 patients. Based on the inclusion criteria, they had at least 2 hand joint contractures (ROM <75%) at the time of their physical examination and undertook to receive physical therapy complex treatment at the Szent András Hospital in Hévíz. The control group received similar complex physical therapy as the study group, as detailed in the methods, but left hands out, meaning they did not receive any therapy for their hands, but instead treated only their spine and large joints (hips, shoulders, knees, and ankles).

At baseline study, we did not find any significant difference between the two SSc groups in any of the clinical parameters.

Physiotherapy consists of 6 treatments: bath in thermal water, healing mud, whirlpool, massage, ergotherapy and exercise therapy, 15 times over a 3-week period.

4.3.2.1 Comparing the outcome measures at baseline and at the end of the 3-week intensive physical therapy, a significant improvement was found in both the interventional and control group in several investigations including DASH, VAS for pain, VAS for Raynaud's syndrome, the result of the delta FTP and the clamping force. Conversely, an improvement in HAQ, DASH, and HAI was found exclusively in the group with active hand therapy compared to controls. The Cochin Hand Functional Scale also showed some improvement in the treated group, but this was not statistically significant.

4.3.2.2 At 6 months after the treatment period, only the results of the hand therapy group showed a sustained improvement ($p < 0.05$) in the HAQ and in the DASH questionnaire. The VAS results for global pain ($p < 0.01$) and Raynaud's syndrome ($p < 0.05$) also showed significant improvement. However, HAI, hand clamping force, and Cochin hand function test did not show any improvement by 6-month in either group.

We compared the study parameters of the patients with good functional status (HAQ <1, n = 20) with the other subgroup with poor functional status (HAQ≥1, n = 11) in the hand therapy group. We found greater improvement ($p < 0.05$) in patients with poorer functional status with HAQ, VAS pain, VAS-Raynaud's syndrome, and delta FTP parameters compared to cases with good HAQ values.

Furthermore, within the hand therapy group, patients whose HAQ change reached the "minimum difference for improvement" (a decrease in HAQ score > 0.14; n = 15) had

significantly lower mean age (56 ± 12years) ($p < 0.05$) compared to those without this particular HAQ improvement (mean age 63 ± 16 years, n = 16). There was no significant difference in disease duration between these particular two study groups. Furthermore, no significant changes were found in the physical and psychological components of the SF-36 in either the hand or control groups.

The treatments were well tolerated by the patients. No unexpected events occurred during the 3-week treatment program of 53 patients. In both groups mild hypertension occurred in some cases, usually within the first two days. In two cases, a mild upper respiratory tract infection was found. No finger ulcer developed in any patient. 3 patients were unable to appear at the 6-month follow-up due to family or work reasons.

5. DISCUSSION

In our clinical follow-up study, we monitored the development of joint contractures for 3 years. We demonstrated that joint contractures develop within the first 4 years and show a significant correlation with the severity of lung fibrosis. We also demonstrated that the extent of movement of the dominant side joints was significantly lower in SSc patients than in the non-dominant side. On the basis of the examination of the upper limb joints, during 3-year follow-up we showed that regular home-based gymnastics performed by our SSc patients was not successful, because although the average joint movement volumes did not deteriorate, the values of the hand functional tests did not show improvement.

Therefore, in a controlled clinical study, we evaluated the effect of complex intensive 3-week hand improvement therapy. The study group received treatment with thermal water and whirlpools, healing mud therapy, ergotherapy, massage and exercise therapy, while the control group received no treatment at all for the hands outside the spa, only for the other parts of the body (spine, lower limbs). Due to the intensive complex physiotherapy, we were able to show an improvement in hand function tests, a reduction in Raynaud's symptoms and pain compared to the control group even after six months.

For comparison, we examined the parameters reflecting hand function and the general health of patients in two immune-mediated disorders, SSc and RA. Objective measurements of hand function showed the worst results in the SSc patient group, whereas the RA patient group showed the worst, weakest values in terms of clamping, pinching, and overall muscle strength compared to the studied SSc population.

We carried out the adaptation of internationally used questionnaires to Hungary and their validation in SSc patients. Translating, adapting the 5 visual analogue scale questions for SSc

patients of Scleroderma Health Assessment Questionnaire (sHAQ), the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire, and the abbreviated QuickDASH Questionnaire psychometric validation for SSc patients can be considered successful. Both tests are quick, simple, and well-defined method for assessing and monitoring the function of upper extremities of SSc patients in everyday clinical practice.

6. NEW RESULTS

6.1 Adaptation and psychometric validation of wellknown international questionnaires

6.1.1 Scleroderma Health Assessment Questionnaire (sHAQ)

- We were the first to apply Scleroderma HAQ in Hungary, its linguistic and cultural adaptation was successful, its reliability showed a high Cronbach-α value.
- We confirmed that sHAQ-DI was worse in patients with more organ involvement than those with less organ manifestations. In addition, patient-reported VAS values were consistent with the severity of the organ failure.
- In the convergent validation examination of the sHAQ, we showed that sHAQ-DI showed a strong correlation primarily with the musculoskeletal function test values, while only a weak correlation was found with the pulmonary, cardiac and skin condition parameters. When evaluating VAS individually, we found a significant correlation between the VAS values and the values characteristic of the given organ involvement.
- It has been pointed out that sHAQ-DI is a good indicator of several organ pathological changes in the disease, but most often shows worse values if the musculoskeletal disorders are significantly damaged.
- Based on our findings, we recommended that the VAS tests of sHAQ be followed separately, as they provide adequate and timely information on the condition of the internal organs and the overall course of the disease.

6.1.2 Validation of the DASH questionnaire in patients with systemic sclerosis

- We were the first in Hungary to use the DASH questionnaire in patients with SSc, which was successful in its linguistic and cultural adaptation.
- Our team was the first in the world to validate DASH and QuickDASH questionnaires in SSc patients. We were able to demonstrate that the upper limb dysfunction of SSc patients is well measured using DASH questionnaires.
- Both questionnaires were significantly correlated with HAQ-DI and also sensitive to changes in upper limb function.

- Discriminant analysis revealed significant differences between results of DASH questionnaires in SSc patients with hand and shoulder contraction and good upper limb movement.
- We pointed out that the impairment of upper limb function is a very important factor in characterizing the general health of SSc patients.

6.2 A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis

- In 131 patients, we determined the range of motion of the 30 movement direction in 10 joints and determined that contracture reduction was 25% or even more.
- We found that, similarly to the data of the literature, small hand joints (82%) were the most affected in the development of contractures in the patients with SSc we examined.
- We have shown that both in lcSSc and in dcSSc patients, contractures develop early, in the first 4 years of the disease.
- We proved that more joint contractures can be expected in the case of more severe condition with higher skin score and/or severe internal organ involvement.
- It has been pointed out that the greater number of contractures found in the dominant (mostly right) joints compared to the non-dominant side may indicate that excessive strain on the joints may result in a deleterious complication and hence reduced mobility.
- For the first time, we have described that the hand damage indexes on the dominant side show worse results in SSc patients.
- Patients' home-based exercise therapy improved the movement of some hand joints, but did not improve hand function during the 3-year follow-up.

6.3 Research focusing on hand function

6.3.1 Comparison of the hand function of patients with systemic sclerosis and rheumatoid arthritis

- The objective measurements of SSc and RA patient group hand function tests showed the worst values in SSc.
- Examination of the clamping and pinching force and general muscular strength as well as subjective questionnaires and indices showed worse and weaker values in the RA patient group.

6.3.2 Efficacy of intensive hand physical therapy in patients with systemic sclerosis

- We found that the combination of a complex, hand-focused 3-week intensive rehabilitation program with exercise therapy, ergotherapy, mud treatment, massage, hydrotherapy in thermal water is effective in improving the hand function of SSc patients in the short and long term.

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