The effect of a 24-week physiotherapy and occupational therapy programme in systemic sclerosis: a monocentric controlled study with follow-up

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Abstract

Objective
The structural and functional changes of the hands and face in systemic sclerosis (SSc) can be severely disabling. We aimed to assess the effect of a 24-week supervised physiotherapy and occupational therapy programme (POTp) combined with home exercise on the function of hands/mouth of SSc patients, compared to a daily home exercise programme in typical outpatient care.

Methods
Fifty-nine patients with SSc were consecutively and non-selectively enrolled in an intervention (IG, n=27) or control (CG, n=32) group. Only the IG underwent the POTp twice a week for 1.5 hours. At baseline, 12, 24, and 48 weeks, all patients were assessed by a blinded physiotherapist for the hands/mouth function (delta finger-to-palm, handgrip strength, Hand and Mobility in Scleroderma, interincisal/interlabial distance), and self-evaluated their hand (Cochin Hand Function Scale) and mouth function (Mouth Handicap in Systemic Sclerosis scale), disability (Health Assessment Questionnaire [HAQ], SSc HAQ), and quality of life (Short Form-36).

Results
At week 24, compared to the significant deterioration in the CG, we found a significant improvement in the IG in the objectively assessed hands/mouth function and in the subjectively evaluated hand function and disability. The improvement was clinically meaningful (by >20%) in a substantial proportion of patients. Although the improvement in most outcomes was still present at week 48, the maximum effect was not sustained.

Conclusion
This 24-week POTp not only attenuated the progressive deterioration, but also significantly improved the function of the hands/mouth, which was clinically meaningful in a substantial proportion of patients with SSc.

Key words
systemic sclerosis, physiotherapy, occupational therapy, dynamometry, hand function, mouth handicap
Physio- and occupational therapy in scleroderma / M. Špiritović et al.

Introduction
Systemic sclerosis (SSc), also called scleroderma, is an immune-mediated connective tissue disease characterised by fibrosis of the skin and internal organs, and vasculopathy (1). Amongst the autoimmune rheumatic diseases, SSc has the highest morbidity and mortality, which is mainly owing to the development of internal organ complications (2). Although the pathogenesis of SSc is slowly being elucidated, and treatment options are improving, scleroderma remains a major medical challenge (1, 3). The improvements in early diagnosis and early aggressive treatment have led to longer survival of patients, increasing the need to intervene against the development of tissue fibrosis and contractures. It is generally recognised that the major rehabilitative problems arise from skin induration and joint and muscle involvement (4). These changes cause prominent disability and are often not thoroughly investigated or treated because of the focus on internal organ complications (1, 2, 4).

Skin involvement is the characteristic feature of SSc which affects the hands and face early and electively, with the potential involvement of all the other skin areas (1, 5). Musculoskeletal involvement in SSc can be an overlooked complication that can manifest as arthralgia, polyarthritis, tendon friction rubs, subcutaneous calcinosis, joint contractures, and myopathy (6). Clinical manifestations in the hands include progressive dermal fibrosis, retraction of the skin, and musculoskeletal involvement, which lead to flexion deformity of the fingers, disabling claw hands, reduced range of motion of the wrist and of radioulnar joints (5). We can observe many characteristic facial features, such as microstomia, microcheilia, radial wrinkles around the mouth, nose sharpening, smoothing of wrinkles, and anamia, which constitute the typical scleroderma face (5, 7). These changes are severely disabling and could affect body image satisfaction, undermine interpersonal relationships, self-esteem, and psychosocial functions, and lead to depression (8, 9). Moreover, they cause difficulties in activities of daily living, particularly due to stiffness and the reduction of grip strength and dexterity, impaired chewing of food, slurred speech, and hindered oral hygiene and dental treatment (7, 10). Consequently, impaired hand function, together with pain and fatigue, could cause work disability, which poses further economic burden on health care and society since the peak incidence of SSc occurs during the highly productive decades of a patient’s working life (7, 11, 12).

The above-mentioned changes in the hands and face are rarely improved by pharmacological therapy and present a window of opportunity for non-pharmacological interventions both to prevent further progression and to mitigate the already established disability, thereby improving the quality of life (5). Indeed, over the past years, rehabilitative treatment of SSc has gained increasing attention. To the best of our knowledge, only three systematic reviews provide a comprehensive overview of the already existing evidence on the effect and safety of non-pharmacological interventions and analyse the quality and limitations of the published studies (13-15). However, the optimal non-pharmacological intervention for SSc patients has yet to be established. Thus, there is an unmet need to provide further evidence on the efficacy and safety justifying non-pharmacological treatment in the routine clinical practice.

Considering the lack of available data on rehabilitative treatment strategies in SSc, we aimed to demonstrate the efficacy of a 24-week intervention combining a personalised physiotherapy and occupational therapy programme (POTp) with home exercise, evidenced by multiple outcome measures reflecting the function of the hands and face compared to the usual outpatient care with home exercise in a substantial number of SSc patients.

Materials and methods

Study design
This prospective, controlled, assessor-blinded, non-randomised, single-centre study (ISRCTN12877295) with follow-up was conducted from May 2014 to June 2017. Ethical approval was obtained from the Ethics Committee of the Institute of Rheumatology in Prague.
The patients’ written informed consent was obtained at enrolment. Patients fulfilling inclusion criteria were consecutively, and non-selectively enrolled from the Institute of Rheumatology and were allocated to an intervention (IG) or control group (CG) based on their ability to adhere to the protocol and the visit schedule of the supervised POTp. All patients were provided with routine care, standard-of-care pharmacological treatment and follow-ups by an attending rheumatologist. At enrolment, all patients were educated on general measures (nutrition, skin warming and protection) and medical information about SSc, and received educational materials for daily home exercise, which represents the standard of non-pharmacologic care in most cases, when a regular proper rehabilitation session is unavailable due to the lack of experienced physiotherapists or occupational therapists with specific skills in treating SSc patients. Only the IG underwent the 24-week individually supervised POTp twice a week for 1.5 hours per session, with a subsequent 24-week follow-up period. CG patients during weeks 0–48 and IG patients during weeks 24–48 were asked to refrain from starting any regular hospital-based non-pharmacological intervention for SSc.

Outcome measures

Primary outcomes included Hand And Mobility In Scleroderma (HAMIS) (16), delta finger-to-palm (∆FTP) (17), handgrip strength (18), maximal mouth opening (inter-labial and inter-incisal distance) (19), Cochin Hand Function Scale (CHFS) (20), and Mouth Handicap In Systemic Sclerosis (MHISS) (21).

Secondary outcomes included the Health Assessment Questionnaire (HAQ) (22), the modified Scleroderma Health Assessment Questionnaire (SSc HAQ) (23), and the Medical Outcomes Study 36-item Short Form Health Survey (SF-36: the physical component score [PCS] and the mental component score [MCS]) (24).

Objectively assessed outcomes were evaluated by an assessor blinded to the intervention. Subjectively assessed outcomes (questionnaires) were self-administered and returned in a sealed envelope by the patients to the blinded assessor. All outcome measures were assessed at baseline and weeks 12, 24, and 48. Further details on the outcome measures, on the inclusion and exclusion criteria, intervention programme, safety and adherence monitoring, clinical and laboratory assessments, and statistical analysis are available in the supplementary material.

Results

Patient inclusion and characteristics

Seventy-five potentially eligible patients who met the inclusion criteria and had no exclusion criteria were contacted (Fig. 1). Fifty-nine of them were willing to adhere to all planned examinations, and were allocated into the IG (mostly patients living in Prague and its proximity, n=27) or the CG (mostly patients living outside of Prague and its proximity, n=32) based on their ability to adhere to the schedule of the 24-week POTp. The study was completed by 25/27 patients in the IG (93%) and 30/32 patients in the CG (94%) (p=1.000). Reasons for discontinuation were work or family circumstances (IG), and malignancy and severe pulmonary arterial hypertension (CG).

The baseline characteristics of all 55 patients included in the analysis are presented in Table I. Although no randomisation was performed, the only significant differences were found in these parameters: CG had a shorter disease duration, and in line with this observation, lower mRSS, higher erythrocyte sedimentation rate (ESR), less frequent interstitial lung disease (ILD), or oesophageal involvement. No significant differences were found in other evaluated parameters (Table I). Since the difference in the prevalence of ILD and dysphagia was not expected to bias the outcome of our POTp, only disease duration, mRSS and ESR were adjusted for in the statistical analysis.

Primary outcomes

In an unadjusted inter-group analysis, we observed significant differences throughout the experimental period in all primary outcomes (i.e. HAMIS, ∆FTP, handgrip strength, maximal mouth opening, CHFS; p<0.001 for all, Supplementary Table S1) with the exception of MHISS (p=0.2977, Suppl. Table S2). These differences were confirmed after adjusting for disease duration, mRSS and ESR (Suppl. Table S1). The adjusted intra-group analysis of
Table I. Clinical and demographic characteristics of scleroderma patients in the intervention group and control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Intervention group (n=25)</th>
<th>Control group (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: female/male, n (%)</td>
<td>22 (88)/3 (12)</td>
<td>26 (87)/4 (13)</td>
<td>0.883</td>
</tr>
<tr>
<td>Age, years</td>
<td>54.0 (50.0 – 59.5)</td>
<td>47.0 (40.0 – 62.3)</td>
<td>0.452</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7.0 (2.7 – 13.5)</td>
<td>4.0 (1.2 – 7.3)</td>
<td>0.026</td>
</tr>
<tr>
<td>SSc subtype, n (%): lcsSsc/deSsc</td>
<td>14 (56)/11 (44)</td>
<td>16 (53)/14 (47)</td>
<td>0.843</td>
</tr>
<tr>
<td>SS-associated symptoms, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILD/PAH/OD/CI/</td>
<td>22 (88)/16 (62)/21 (84)/13/2 (7)</td>
<td>16 (53)/3 (10)/16 (53)/1 (3)</td>
<td>0.017/0.704/0.023/0.330/0.398/0.679/0.931/1.000/0.499/1.000</td>
</tr>
<tr>
<td>R/PR/PU/CA/</td>
<td>4 (16)/24 (96)/6 (21)/4 (4)</td>
<td>2 (7)/29 (97)/8 (27)/1 (3)</td>
<td>0.398/0.679/0.931/1.000/0.499/1.000</td>
</tr>
<tr>
<td>AI/S/A</td>
<td>0 (0)/25 (100)</td>
<td>2 (7)/25 (100)</td>
<td>0.499/1.000</td>
</tr>
<tr>
<td>ESSG activity index</td>
<td>3.0 (1.5 – 4.0)</td>
<td>2.3 (1.0 – 3.5)</td>
<td>0.171</td>
</tr>
<tr>
<td>mRSS</td>
<td>16.0 (11.0 – 29.5)</td>
<td>10.0 (3.5 – 15.3)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Laboratory features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibodies, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA/Sc70/ACA</td>
<td>25 (100)/17 (68)/3 (12)</td>
<td>30 (100)/20 (67)/6 (20)</td>
<td>1.000/1.000/0.489</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.1 (0.9 – 6.9)</td>
<td>4.9 (1.9 – 9.6)</td>
<td>0.128</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>11.0 (6.0 – 21.0)</td>
<td>21.0 (13.0 – 33.0)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Current treatment, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC/MTX/CPA/AZA/MMF</td>
<td>5 (20)/3 (12)/2 (8)/8 (33)/1 (4)</td>
<td>13 (43)/4 (13)/8 (27)/3 (10)/0 (0)</td>
<td>0.147/0.966/0.159/0.176/0.449</td>
</tr>
</tbody>
</table>

Data are presented as median (inter-quartile range) unless stated otherwise. Statistically significant differences (p<0.05) are marked in bold.

SSc: systemic sclerosis; lcsSsc: limited cutaneous SSc; dcsSsc: diffuse cutaneous SSc; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; OD: oesophageal dysmotility; CI: cardiac involvement; RI: renal involvement; PR: Raynaud’s phenomenon; DU: digital ulceration; CA: calcification; A: arthritis; SI: skin involvement; ANA: antinuclear antibodies; Sc70: anti-DNA-topoisomerase I antibodies; ACA: anticentromere antibodies; ESSG: European Scleroderma Study Group; mRSS: modified Rodnan skin score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GC: low dose glucocorticoids (i.e. ≤10 mg/day of prednisone); MTX: methotrexate; CPA: cyclophosphamide; AZA: azathioprine; MMF: mycophenolate mofetil.

Objectively assessed hand function (i.e. HAMIS, ∆FTPl, handgrip strength) in the IG demonstrated a significant improvement over the first 12 weeks of the POTp (p≤0.001 for all except for ∆FTPl of the dominant hand with a borderline p=0.0757), as well as over the entire 24-week POTp (p<0.001 for all) (Fig. 2 A, C, E, Suppl. Table S1). Whereas in the CG, we found a significant progressive deterioration (p<0.05 for all except for ∆FTPl of the dominant hand with a borderline p=0.1062) over weeks 0-24 (Fig. 2 A, C, E, Suppl. Table S1). The improvement in the IG over the 24-week POTp was clinically meaningful (i.e. a 24-week improvement by >20%, inspired by American College of Rheumatology Response Criteri...
group analysis were found for subjectively evaluated general function/disability (HAQ: $p=0.3519$) and quality of life (SF-36 PCS: $p=0.9412$; SF-36 MCS: $p=0.5770$) (Suppl. Table S2). The adjusted intra-group analysis of SSc HAQ and SSc HAQ-VAS in the IG showed a significant improvement only in SSc HAQ at week 12 ($p=0.0416$) (Fig. 4 C, E, Suppl. Table S1). Interestingly, these parameters improved only over weeks 0-12, and this improvement
was sustained throughout the remaining experimental period. Whereas in the CG, we found a numerical trend towards deterioration over weeks 0–24 (SSc HAQ-V AS: \( p = 0.0731 \); SSc HAQ: \( p = 0.0963 \)), which missed the level of statistical significance (Fig. 4 C, E, Suppl. Table S1). A substantial proportion of IG patients achieved clinically meaningful improvement over weeks 0–24 (SSc HAQ-V AS: 56%, SSc HAQ: 32%) (Fig. 4 D, F). No significant differences in either group were found over weeks 24–48 (\( p > 0.05 \) for all) (Fig. 4 C, E, Suppl. Table S1).

Unadjusted intra-group analyses did not reveal any significant differences between any intervals of interest in either group for HAQ, SF-36 PCS and MCS (\( p > 0.05 \) for all) with the exception of a trend towards improvement in SF-36 MCS in the IG over weeks 0–12 (\( p = 0.0524 \)), which barely missed the level of statistical significance.

**Adverse events and adherence to the intervention**

During the 24-week POTp, 7/27 (26%) patients in the IG had the following adverse events: conjunctivitis (n=1), aggravated reflux (n=1), diarrhoea/constipation (n=3) and skin ulcers in the lower leg (n=2). None of these events were related to the POTp. These complications were successfully treated, which enabled them to continue with the POTp without interruption. All patients in the IG tolerated the POTp well. No signs of clinically relevant deterioration (e.g. increased skin thickening or inflammation, tendonitis, development of digital ulcers or skin calcifications) were observed, and no changes in the use of analgesics were recorded. No substantially increased levels of pain, dyspnoea or exertion assessed by visual analogue scales (VAS) in the diaries monitoring the performance of home exercise were recorded.

Of the 27 patients, who started the POTp, two (7%) were unable to complete the 24-week POTp due to work constraints (n=1) and family circumstances (n=1). All of the 25 patients, who completed the 24-week POTp, attended all 48 of the planned supervised sessions. In 12 of these patients (48%), 1–6 sessions needed to be rescheduled and substituted on the next possible day due to patients’ unavailability.
Fig. 4. Subjectively evaluated hand function and scleroderma-related function/disability in the intervention group and control group. The 24-week intervention significantly improved hand function (Cochin Hand Function Scale) (A), scleroderma-related function/disability assessed by Systemic Sclerosis (SSc) Health Assessment Questionnaire (HAQ) Visual Analogue Scales (C) and global SSc HAQ (E), and prevented their progressive deterioration. The difference in the percentage distribution of improvement/deterioration over weeks 0-24 was significant for all parameters (B, D, F, respectively). The lines represent the mean, and whiskers represent the standard error of the mean.

w: week; p*: unadjusted inter-group comparison; p: unadjusted intra-group comparison in black (intervention group) and grey (control group); p†: difference in overall distribution; p‡: difference in clinically meaningful improvement.
caused by work (65%) or family (35%) circumstances.

**Discussion**

Given the heterogeneity of interventions, their focus on hands and/or face and the outcomes assessed in the published non-pharmacological intervention programmes for SSc (13-15), it is not possible to directly compare the results. According to the top 23 published studies ranked by methodological quality in the systematic review by Willems et al. (13), particularly those related to our POTp, the duration and frequency ranged from 12–24 weeks, 1-2 times per day for 2–15 minutes per session in studies focused on mouth function (19, 26, 27), and 9–12 weeks, 1–2 sessions per week for 1 hour each in studies focusing on hand and/or mouth function (18, 28-30), including one study (31) of two weeks of daily supervised 30-minute intervention. Five out of these eight studies were randomised controlled trials, which recruited 20-40 patients each (19, 28-30), or 53 patients in (18). The remaining two were observational studies with no available control group, comprising 17 (26) and ten patients (27), and the last one was a non-randomised controlled trial involving 33 patients (31). The mean or median disease duration in these SSc patients ranged from 6–15 years (18, 19, 27-31). Significantly shorter disease duration in our CG, associated with lower mRSS and higher ESR, was most probably underlying the overall better baseline levels of most outcomes and their progressive deterioration, since patients in early stages of SSc are prone to the more rapid development of skin and musculoskeletal involvement compared to patients in later stages (1, 4-6). However, the deterioration in most parameters in the CG over weeks 0–24 and 0–48 remained statistically significant even after adjusting for disease duration, mRSS, and ESR. Nevertheless, these findings emphasise that non-pharmacological interventions should be commenced early in the disease to prevent the initial progressive deterioration of hand and mouth function and overall disability. Interestingly, only Yuen et al. (19) and Schouffer et al. (18) employed an inter-group analysis, with the latter study also applying correction for baseline values (18). None of these eight studies assessed the clinically meaningful change of all outcome measures. In our study, there were no restrictions to the standard-of-care medication due to the very long duration of our study and the character of the disease. However, both the unadjusted and adjusted analyses revealed no statistically significant differences between the IG and CG over weeks 0–24 and 0–48 in the administration of conventional synthetic antirheumatic drugs or glucocorticoids (data not shown). Thus, even though the contribution of pharmacological therapy to the observed benefits of our POTp in the IG cannot be estimated, the conditions regarding pharmacological therapy in both groups were comparable and should not affect the inter-group comparisons of outcomes. In addition, results from our study thus represent the real-life data which are applicable to everyday routine clinical practice.

Since there is no golden standard to assess the effect of the non-pharmacological intervention in SSc patients, we used several primary and secondary outcomes. In line with our findings of improvement in hand function, these outcomes improved to a different extent also in other studies, including HAMIS in (18, 28, 29, 31), fist closure in (28, 29), handgrip strength in (18), and CHFS in (28, 29). Significant improvement in maximal mouth opening, similar to our findings, was observed to a varying extent in other studies (18, 19, 26, 27, 29, 30). In our study, we detected only a numerical trend towards improvement in the IG over the 24-week POTp in MHISS, which was statistically non-significant (mean difference -2.24, p=0.1198). In contrast, Maddali-Bongi et al. (30) demonstrated a significant improvement in MHISS over weeks 0–9 (mean difference -0.95, p=0.001), which was, however, comparable to the mean difference detected in our study over weeks 0–12 in the IG (mean difference -1.44, p=0.1172), albeit statistically non-significant, probably due to larger variability. Similar to our findings, SSc HAQ significantly improved also in one study (18). In our study, we did not find any significant change in HAQ, which is in line with the findings in one study (30) but in contrast with significant improvement in other studies (28, 29). We presume that it is more difficult to achieve an improvement in overall disability in patients with less disability at baseline: mean baseline HAQ was 0.80 in our study (p>0.05 for both over weeks 0–12 and 0–24), 0.50 (p>0.05 over weeks 0–9) in (30), 1.20 (p<0.05 over weeks 0–9) in (29), and 0.94 (p<0.05 over weeks 0–9) in (28). Regarding the quality of life, in our study, we observed a borderline non-significant trend towards improvement in SF-36 MCS over weeks 0–12, which was sustained over weeks 12–48, whereas no significant changes were found in SF-36 PCS. Similarly, no significant differences were found in two studies (18, 30), whereas two other studies detected a significant improvement in both scores over their 9-week intervention (28, 29). Furthermore, although the improvement of most outcomes in our IG was still present at week 48, the maximum effects from week 24 were not sustained, most probably due to the absence of regular professional supervision and motivation. This finding is in line with other studies demonstrating loss of achieved benefits in most outcomes during the follow-up period (18, 29), and emphasises the necessity of a continuous and regularly supervised non-pharmacological intervention to prevent further progression of disability. In addition, a closer observation of our raw data and their intra-group analysis in the IG revealed a more considerable improvement in most parameters over the first 12 weeks, probably due to an initiation effect and a ceiling effect.

**Limitations**

Our study has several limitations. Firstly, it was a non-randomised controlled study due to several aspects associated with the design and aims of our study, such as unprecedentedly long supervised intervention (24 weeks), with an extended follow-up (24 weeks), on
an exceptionally large recruitment target number of patients (n=25–30 per group) with a rare disease fulfilling the inclusion criteria; and we wanted to provide our POTp to as many suitable patients as possible. We addressed the potential selection and allocation bias by consecutive non-selective recruitment, by using a blinded assessor, and by adjusting for significantly different baseline variables. Secondly, the standard-of-care background medical therapy was allowed due to the very long duration of the study and the character of the disease, and because we aimed to provide evidence for our POTp from a real-life clinical practice for practical routine use. Thirdly, the sample size did not allow for subgroup analysis to characterise those with the largest improvements. Lastly, since our POTp combined several different interventions, we cannot assess which individual component contributed most to the overall effect.

Conclusions
This 24-week supervised, tailored physiotherapy and occupational therapy programme for SSc patients not only altered the natural course of progressive deterioration of the function of the hands and mouth observed in the control group, but also resulted in a significant improvement in both objectively and subjectively evaluated measures of hand and mouth function and global disability specific to SSc. The achieved improvement in hand function and global disability was clinically meaningful in a substantial proportion of SSc patients. Although the improvement of most assessed outcome measures in the intervention group was still present at the end of the follow-up period, the maximum effects were not sustained, most probably due to the absence of regular professional supervision and motivation. Our results provide substantial evidence derived from a solid number of SSc patients from routine clinical practice, and further support the vital role of non-pharmacological interventions in multidisciplinary care for patients with SSc. Our findings emphasise the necessity of early commencement of continuous and regularly supervised physiotherapy and occupational therapy in order to prevent further progression and to reduce the already established disability.

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References


