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ORIGINAL ARTICLE

An individualized rehabilitation program in patients with systemic sclerosis may improve quality of life and hand mobility

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Abstract Few data are available to assess the efficacy of rehabilitative interventions in systemic sclerosis (SSc). We refer here the results of an individualized rehabilitation program in 16 patients with SSc. In particular, when possible, the number of patients who achieved a minimal clinically important difference (MCID) was determined. Results were evaluated taking advantage of the development of validated questionnaires and tests to assess quality of life (QOL) and disability in SSc. At the end of a period of 4 months of observation, 69% and 62% of patients reported an improvement of the physical and mental components of the SF-36 higher than the MCID (as established in other rheumatic conditions). Analogously, an improvement of the impact of respiratory disease on patients' QOL, as assessed by the Saint George's Respiratory Questionnaire, was perceived by 67% of them. These results might be explained by better exercise tolerance, which was suggested by the significant reduction of the heart rate and of a visual analogue scale for dyspnoea at the end of the 6-min walking test. Finally, a statistically significant improvement of hand mobility, as assessed by the hand mobility in scleroderma test was obtained. This study suggests that a significant proportion of patients with SSc experience an improvement in their perception of QOL, a better exercise tolerance, and a better hand mobility after a rehabilitation program consisting by a 2-week period of daily individual 30-min sessions as outpatient, followed by at-home exercise program.

Keywords Rehabilitation · Saint George's respiratory questionnaire · SF-36 · Systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease, characterized by endothelium injury, immune activation, and collagen deposition by activated fibroblasts, leading to generalized microangiopathy and fibrosis of the skin and internal organs [1]. Patients with SSc suffer from reduced quality of life (QOL) and disability, caused by skin, joint, muscle, and internal organs involvement [2, 3].

Despite recent improvements in diagnosis and treatment, in most patients, the disease follows a chronic course with an increasing burden of organ damage and disability. Intervention against the development of fibrosis and contractures is, therefore, needed, and it might include appropriate rehabilitation programs [4, 5]. However, few data are available in the literature to assess the efficacy of such interventions [4, 5].

The aim of the present study was to evaluate the results on an individualized rehabilitation program in 16 patients with SSc. For this purpose, validated questionnaires and tests to assess QOL and disability in SSc were used [6]. In particular, when possible, the number of patients who achieved a minimal clinically important difference (MCID) defined as the smallest difference in score of a measure of

interest that patients perceive as beneficial [7] was determined.

Materials and methods

Patients and controls

Ninety consecutive patients with a diagnosis of SSc made according to the criteria of LeRoy [8], who attended our outpatient clinic for periodic controls or Daycare for infusive therapies, were evaluated in order to participate in a rehabilitation program if they fulfilled the following inclusion criteria: age 18–75 years; stable disease; no change in antirheumatic treatment in the three previous months; none of the following: inability to perform the rehabilitation program due to skeletal–muscle impairment or other illness; presence of other diseases interfering with the performance of daily activities; pulmonary hypertension on echocardiogram, defined as a right-ventricular systolic pressure >45 mmHg; psychiatric disorders including alcohol and drugs abuse; pregnancy or planned pregnancy in the next 6 months. Patients fulfilling these criteria were asked with a written document to participate in the rehabilitation program and to provide anyway their written informed consent for data treatment.

Four patients were excluded based on predetermined criteria, and 86 were asked to participate. Fifty-six patients denied consent: they did not differ from the other patients as far as their clinical and demographic parameters (data not shown). The most frequent reason for refusing the study was inability to reach every day the hospital to engage in the 2-week rehabilitation program. Thirty patients (35%) volunteered to participate in the study. Sixteen of these 30 patients were finally treated, while the others were put in a waiting list. Seventeen patients of the 56 patients not participating in the program nevertheless volunteered to be evaluated with the same tests at the same time intervals and served as controls. The main demographic and clinical characteristics of the 16 treated patients (herefrom defined as cases) and of the 17 controls are shown in Table 1.

Most patients received Calcium-channel blockers or other vasodilators and low-dose aspirin. Among cases, seven patients were treated with low-dose corticosteroids (prednisone—4–10 mg/day). Three patients have previously received intravenous Cyclophosphamide for active ILD, as described [9], and two of them were still receiving oral azathioprine at the moment of the study. Two patients with severe ischemic ulcers were treated with intravenous cyclic iloprost, as described [10].

Controls were recruited mainly among patients who needed frequent evaluations in our outpatient clinic or infusive therapy with iloprost (n=14; p=0.0001, as compared with the cohort of cases), but there was no other difference with cases, as far as treatments received. Therefore, they suffered from a more severe disease than cases, as shown by reduced lung function tests and by a higher, although not significantly, incidence of active ischemic digital ulcers at the moment of the study (Table 1).

Rehabilitation program

After the initial evaluation (T0), the rehabilitation program consisted of ten individual sessions of 30 min. Each session included warm-up and cool-down exercises, training of motor functions, and respiratory exercises (diaphragmatic breathing and controlled coughing). The program of lower-extremity exercises was based on a combination of treadmill and free-walking, whereas upper-extremity exercises included a combination of finger-stretching exercises and occupational therapy. Physical therapy was also prescribed to 13 patients with articular problems. In particular, seven patients were treated with transcutaneous electrical nerve stimulation, three with magnetic fields therapy, two with laser therapy, one with radar therapy, and one with extracorporeal shock waves. In eight patients with puffy hands, ultrasound immersion therapy was prescribed.

At-home exercise programs were also prescribed to be completed on days when the program was terminated. Patients were asked to keep a diary of activities, which was reviewed by the rehabilitation coordinator at each visit.

Patients were reevaluated after 2 (T2) and 4 months (T4). At each visit, they were asked for compliance with the home-treatment program, and to answer to self-administered questionnaires evaluating disability and self-perceived health-related QOL, both in general terms and as determined by respiratory symptoms. Functional tests exploring hand mobility and physical activity were performed. Moreover, at the initial and final visit, lung function tests and skin thickness were evaluated.

Outcome measures

Health Assessment Questionnaire Disability Index [11] It was evaluated using the Italian version [12]. This questionnaire contains 20 items, each assessed on a 0 (lack of disability) to 3 (complete disability) scale. These are divided into eight domains; the highest scores in each of the eight domains are summed and divided by 8 to calculate the general disability index. The MCID in the Health Assessment Questionnaire Disability Index (HAQ-DI) in patients with SSc has been estimated to be 0.14 [13].

Short Form 36 [14] It was evaluated using the Italian version [15]. This questionnaire contains 36 items, measuring health on eight dimensions: General Health

Table 1 Main clinical and demographic characteristic of patients treated with a rehabilitative program (cases) and controls

	Cases (n=16)	Controls (n=17)	P value
Age (years)	66.5 [63.0–70.5]	57 [50–67]	ns
Gender	16 female	16 female, 1 male	ns
Disease duration (years)	14.5 [10–21]	9 [5–13]	ns
Time from the onset of Raynaud's phenomenon (years)	17 [11–22]	14.5 [9–36]	ns
Disease subset	4 dcSSc (25%) 12 lcSSc (75%)	6 dcSSc 11 lcSSc	ns
Rodnan skin score	6 [4–9]	8 [3–11]	ns
Autoantibodies	ANA: 16/16 ACA: 6/16 Anti-Topo I: 6/16	ANA: 17/17 Aca: 6/17 Anti-Topo I: 5/17	ns
FVC	111% [101%-133%]	93% [64–119]	<0.001
DLCO	70% [56%-80%]	59% [37–74]	<0.001
Interstitial lung disease	7 (43%)	9 (53%)	ns
Ischaemic digital ulcers	3 (19%)	7 (41%)	ns

Data are expressed as the median [25th–75th percentile]
ns Not significant

perception, Physical and Social Functioning, Role Limitations by Physical or Emotional Problems, Mental Health, Vitality, and Bodily Pain. For each dimension, items are coded, summed, and transformed on to a scale from 0 (worst health) to 100 (best health). These eight dimensions can be reduced to two summary measures, a physical component score (PCS) and a mental component score (MCS). These were standardized to have a mean of 50 and a standard deviation of 10 in a population of 1032 healthy Italian women [16]. The MCID in the short form 36 (SF-36) have been estimated in patients with rheumatoid arthritis [17].

Saint George's Respiratory Questionnaire It is a standardized, self-administered questionnaire for measuring impaired health and perceived QOL in airways disease, which has been validated in patients with SSc [18]. It consists of 76 items, producing a "symptoms," an "activity," an "impact," and a "total score." Scores can range from 0 (no impairment) to 100 (the worst impairment) for each component; higher scores connote greater distress and, thus worse, QOL. The Italian version was used [19]. The MCID in the Saint George's Respiratory Questionnaire (SGRQ) in patients with in patients with chronic obstructive lung disease is −4%. [20].

Hand Mobility in Scleroderma It is a hand function test for patients with SSc [21]. It consists of nine items, assessing the movements included in an ordinary range of motion test. Each exercise is graded on a 0–3 scale, where 0 corresponds to normal function and 3 denotes that the individual is unable to perform the task.

6-min walking test It measures the distance a patient can quickly walk on a flat, hard surface in a period of 6 min and is thought to reflect well a person's functional activity level for daily physical activities. It was conducted according to the American Thoracic Society guidelines [22]. The MCID in the 6-min walking test (6MWT) in patients with chronic lung disease is 54 m [23]. Before and after the test, the modified Borg Dyspnoea Scale score [24] for perceived breathlessness was measured. This was developed to provide a method of rating perceived exertion on a scale of with various points on the scale "anchored" to verbal descriptions. It was described as showing a close correlation with measures of blood lactate and muscle lactate, and it is, therefore, thought to be influenced by muscular fatigue. The MCID in the Borg scale in patients with is 1 point [25]. Moreover, patients completed a 10-point visual analog scale (VAS), in which 0 represented no dyspnoea and 10 represented intolerable dyspnoea. Two icons helped patients in interpreting this VAS [26].

Lung function tests FVC and diffusion lung capacity for carbon monoxide (DLCO) were evaluated by standard procedures and results were expressed as percentages of predicted values based on age, sex, and height. Normal values were calculated by reference standard provided by the European Coal and Steel community [27, 28].

Skin score The skin was assessed according to the modified Rodnan Skin thickness Score (RSS), which has acceptable inter- and intra-observer reliability [29].

Statistical analysis

Data were expressed as the median (25th–75th percentile). The variations of outcome measures within times were compared using the Wilcoxon signed rank test. To assess differences between groups, Mann–Whitney U test and Fisher's exact test were applied for continuous and

dichotomous variables, respectively. All tests were two-tailed. Statistical significance was set at $p=0.05$, not corrected for multiple analyses.

Statistical analysis was performed using StatView 5.0.1 (SAS Institute, Cary, NC, USA).

Results

In the cohort of treated patients, there was a moderate disability, as shown by the HAQ-DI. This was progressively, but not significantly, reduced within the time of observation (Table 2). However, four out of 16 patients (25%) had an improvement higher than −0.14, which is considered the MCID in patients with SSc [13], whereas only one patient (6%) had a relevant worsening.

The QOL, as assessed by the SF-36 questionnaire, was reduced in this cohort, particularly as far as the Physical Component (see Table 3). After rehabilitation, at T4, items assessing General Health, Physical and Social Functioning, Bodily Pain, and Mental Health were significantly improved. Accordingly, both the summary scales of the SF-36 (PCS and MCS) were improved (Table 3). There is no definition of a MCID in the SF36 scales in patients with SSc. Using the changes that estimated the probability of a such a result in patients with rheumatoid arthritis [17], we observed an improvement across the different scores, in a variable proportion of patients, ranging from 25% (Mental Health) to 81% (General Health), while only occasional patients had significant worsening (Fig. 1). Accordingly, 69% and 62% of patients had an improvement of the PCS and the MCS higher than the estimated MCID, whereas only occasional patients had a significant deterioration.

Seven out of 16 patients suffered from ILD, as demonstrated by chest X-rays or HRCT (Table 1). Accordingly, the basal median DLCO in this series was reduced (Table 1), and QOL determined by airway symptoms, as assessed by total SGRQ, showed a level of clinically significant compromise (>10 points) in all the patients, particularly in the activity score (Table 4), which measures the patients' current disturbance to perform daily physical activity. There was a statistically significant improvement of all the four components of the SGRQ during the period of observation. An improvement of four units for each of the SGRQ scores appears to be a reliable MCID in patients with chronic obstructive lung diseases [20]. Using this threshold, ten out of 15 evaluable patients (67%) were significantly improved in the total SGRQ score at the end of the observation (60%, 67%, and 47% in the "activity," "symptoms," and "impact" scores, respectively), whereas only one patient was significantly worsened.

HAMIS test disclosed a limitation of hand mobility in our patients, which was significantly improved during the rehabilitation program (Table 5).

There was no variation in the 6MWT from T0 (343 m [289–409]) to T4 (330 m [300–410]). However, improvement of some parameters at the end of 6MWT was observed: heart rate decreased (from T0: 89 [88–96] to T4: 80 [74–84] $p=0.019$), the VAS for dyspnoea decreased (from 5.5 [3.8–6.3] at T0 to 4.0 [1.5–5] at T4; $p=0.05$), whereas the Borg score improved, but not at a statistically significant level, from 3.5 [2.8–5.3] at T0 to 3.0 [0–5] at T4. However, six out of 16 patients (38%) had an improvement of the Borg Score higher than −1, which is considered the MCID in patients with chronic obstructive lung disease [26], whereas only two patients (12%) had a relevant worsening.

There was no statistical variation in lung function tests and mRSS during the time of observation (data not shown).

Controls had a higher baseline HAQ-DI (0.87 [0.62–2]) than cases ($p=0.009$), probably because of a more severe disease with frequent digital ulcers (Table 1). However, no other significant difference in the baseline outcome measures was observed among the two groups.

At the end of a 4-month period, in the control group there was no significant improvement in any of the outcome measures. Conversely, there was a minimal worsening of the Borg score ($p=0.045$).

Table 2 Variations of the Health Assessment Questionnaire- Disability Index in patients treated with a rehabilitative program

	T0	T2	T4	*P* value
HAQ-DI	0.63 [0.34–0.75]	0.56 [0.34–0.88]	0.44 [0.25–0.75]	ns

Data are expressed as the median [25th–75th percentile]
ns Not significant

Discussion

SSc is a serious auto-immune disease, which, despite recent advances in medical treatment, considerably decreases physical functioning and overall QOL, particularly because of skin, joint, and lung involvement. Although in many other rheumatic conditions, including rare diseases like dermato-polymyositis and systemic lupus erythematosus [30, 31], the effectiveness of exercise therapy has been established; research in this area is virtually absent in SSc. Indeed, the one available review was merely based on opinions and experience, whereas controlled trials were nearly absent [4]. Active and carefully executed passive range of motion exercises, with the aim of stretching the

Table 3 Variations of the Short Form 36 in patients treated with a rehabilitative program

SF-36	Median [25th–75th percentile]			*P* (Wilcoxon signed rank test)		
	T0	T2	T4	T0–T2	T2–T4	T0–T4
General health	32.5 (25–40)	32.5 (25–46.3)	42.5 (33.8–75)	ns	0.014	0.004
Physical functioning	55.0 (33.8–71.3)	55.0 (25–66.3)	75.0 (58.8–81.3)	ns	0.004	0.003
Role—physical	12.5 (0–50)	50.0 (0–100)	50.0 (25–75)	ns	ns	ns
Role—emotional	33.3 (25–75)	33.3 (0–75)	100 (0–100)	ns	0.028	ns
Social functioning	62.5 (46.9–87.5))	57.3 (50–87.5)	87.5 (75–100)	ns	0.023	0.015
Bodily pain	41.0 (31.8–54.5)	41.0 (41–61.3)	66.5 (41–74)	ns	ns	0.023
Vitality	52.5 (41.3–60)	55.0 (38.8–61.3)	50.0 (43.8–71.3)	ns	ns	ns
Mental health	55.0 (39–72)	57.0 (50–6.5)	66.0 (53.5–78)	ns	ns	0.05
PCS	39.8 (33.9–42)	40.1 (35.6–43.5)	44.0 (41.5–48)	ns	0.005	0.001
MCS	46.5 (42.2–49.2)	46.3 (40.5–50.6)	50.4 (46–54.3)	ns	0.004	0.013

Data are expressed as the median [25th-75th percentile]
ns Not significant, *PCS* physical component score, *MCS* mental component score

skin and periarticular structures, and exercises to improve muscle functioning or aerobic capacity were advocated [4]. Recently, hand exercises in combination with paraffin baths were found to improve mobility, perceived stiffness, and skin elasticity [32]. In addition, the effectiveness of mouth opening exercises regarding eating, speaking, and oral hygiene was documented [33]. As far as physical therapies, only uncontrolled data concerning very small numbers of patients are available.

In this study, we evaluated a cohort of 16 patients with SSc, which suffered from a reduction of their physical function and QOL similar to those reported by others and us in larger series [11, 16, 18, 34]. At the end of a 4-month period, 62% of patients reported an improvement of both the main components of the SF-36 that was higher than the MCID (as established in other rheumatic conditions). Analogously, an improvement of the impact of respiratory disease on patients' QOL, as assessed by the SGRQ, was perceived by 67% of them. These results might be explained by better exercise tolerance, which was suggested by the significant reduction of the heart rate and of a VAS for dyspnoea at the end of the 6MWT. Finally, a statistically significant improvement of hand mobility, as assessed by the HAMIS test, was obtained.

Based on these results, this study suggests that a significant proportion of patients with SSc might experience an improvement in their perception of QOL, a better exercise tolerance, and a better hand mobility after a rehabilitation program consisting by a 2-week period of daily 30-min individual sessions as outpatient, followed by at-home exercise program.

There are several limitations in the present study, including the individualization of the rehabilitative and physical therapy, the lack of a blinded control group, the

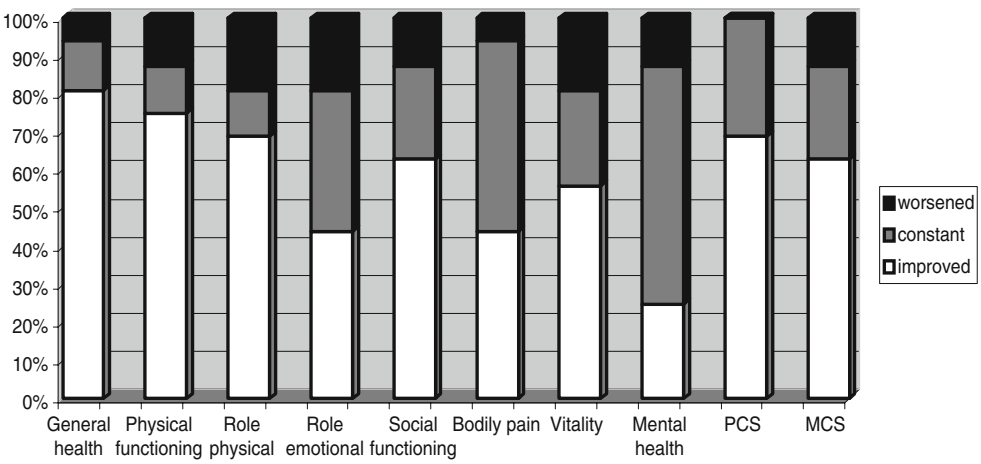

Fig. 1 An improvement across the different scores, in a variable proportion of patients, ranging from 25% (Mental Health) to 81% (General Health), while only occasional patients had significant worsening. Accordingly, 69% and 62% of patients had an improvement of the PCS and the MCS higher than the estimated MCID, whereas only occasional patients had a significant deterioration

Table 4 Variations of the Saint George's Respiratory Questionnaire in patients treated with a rehabilitative program

SGRQ	Median [25th–75th percentile]			*P* (Wilcoxon signed rank test)		
	T0	T2	T4	T0-T2	T2-T4	T0-T4
Symptoms	15.8 (8–29.9)	11.9 (8.4–30.1)	4.4 (0–12.5)	ns	0.008	0.003
Activity	59.5 (38.7–60.1)	53.2 (41.4–63.2)	47.3 (35.8–58)	ns	ns	0.01
Impact	19.7 (4.1–37.3)	17.3 (7–35.1)	12.1 (3.9–18.5)	ns	0.046	0.05
TOTAL	30.9 (17.3–36.9)	29.2 (16.2–37.1)	22.7 (12.5–31.3)	ns	0.016	0.012

Data are expressed as the median [25th–75th percentile]
ns Not significant

very small number of patients included and the relatively short period of follow-up.

However, patients with SSc included in the present study, like those in every cohort of patients with such a polymorphic disease, were largely heterogeneous in their clinical characteristics, QOL limitations, and needs. Although, from a methodological viewpoint, conducting various randomized clinical trials, each concerning one single non-pharmacological intervention, would be a better strategy, considering the rarity of SSc [35], this would be a very difficult task. Moreover, in daily practice, various non-pharmacological interventions are often combined, by means of "ad hoc" patient care programs. So we preferred an alternative scientific approach, evaluating the effectiveness of an "optimal" treatment program.

We did not observe significant variations of the outcome measures evaluated in the present study in a control parallel series of patients who did not participate in the rehabilitation program but were evaluated with the same tests at the same time intervals. This suggests that the observed variation were not due to chance alone. However, it cannot be excluded that the observed improvements were due to observer or patient bias. Only blind studies could exclude such bias, but these are not feasible for rehabilitation programs. An observer-blinded study could exclude bias in observer-dependent measures, but, among the items improved in the present study, only the HAMIS was observer-dependant. It should be kept in mind that patients' expectations might have been influenced by their willingness to participate in the study and that these factors might have influenced the study results with a placebo effect. Interestingly, however, in most of the parameters evaluated, the improvement was delayed, being higher in the period from T2 to T4 (Table, when patients performed only at-home exercise, than in the first 2 months of observation, which included the period of treatment in the Clinic, in which a higher placebo effect was expected).

Finally, although limited, the number of enrolled patients and the length of follow-up of this study compare favorably with the scanty available date concerning rehabilitation in SSc [32, 33]. Although the conclusion of our study cannot be robust and the small number of cases precludes the possibility for subgroup analysis, the results here presented might encourage further research in such a neglected area. We suggest, therefore, that prospective trials enrolling a higher number of patients and a longer follow-up may be warranted to appropriately evaluate the utility of this treatment in SSc.

Disclosures None.

Table 5 Variations of the HAMIS test in patients treated with a rehabilitative program

HAMIS test	Median [25th–75th percentile]			*P* (Wilcoxon signed rank test)		
	T0	T2	T4	T0–T2	T2–T4	T0–T4
Right hand	3.0 (2.5–4.5)	3.0 (2–4)	2.0 (0.5–2.5)	ns	0.005	0.002
Left hand	3.0 (2.5–4)	3.0 (1–3.5)	1.0 (0–3)	ns	0.008	0.003

Data are expressed as the median [25th–75th percentile]
ns Not significant

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